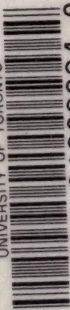


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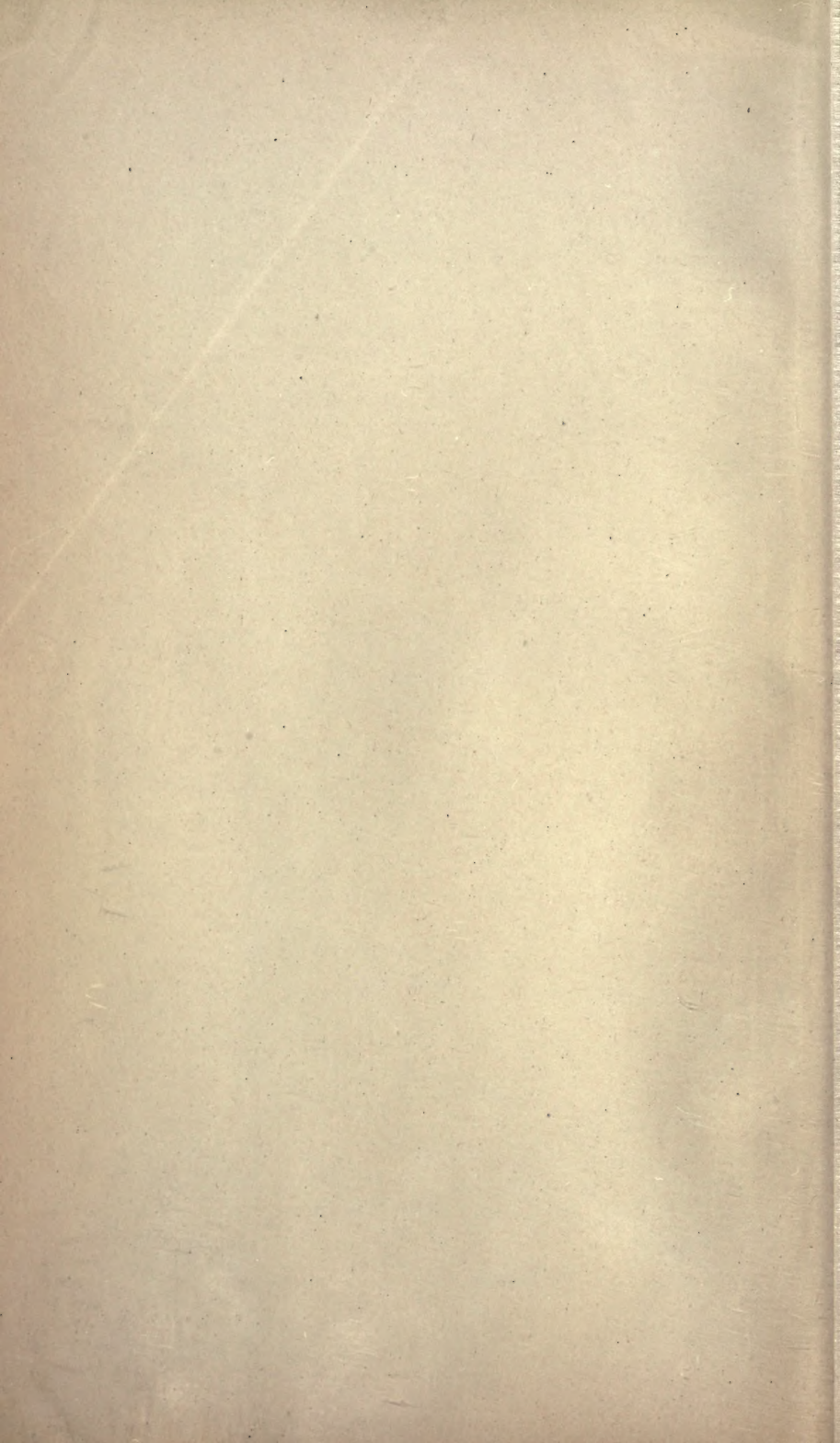
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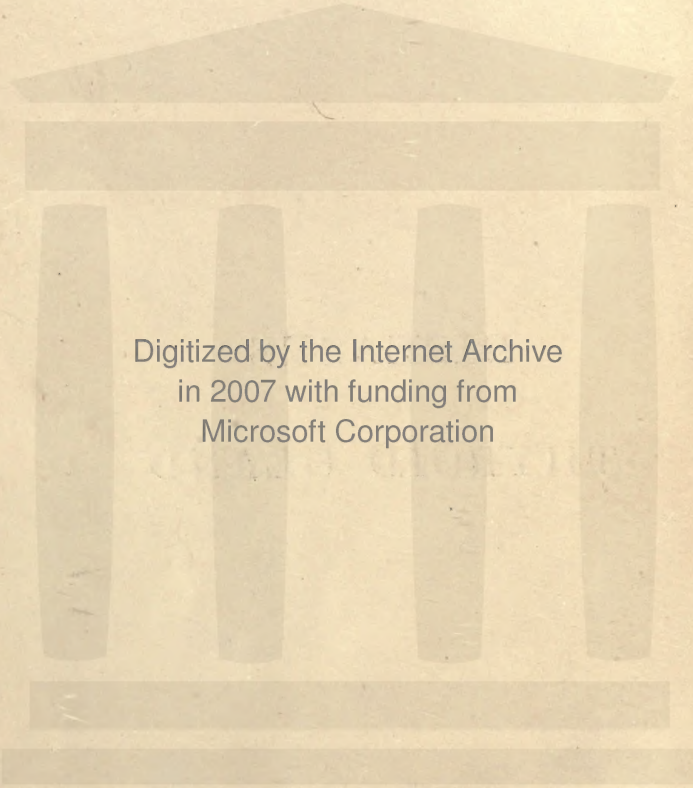
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CATALOG



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DISEASES
OF THE
THYROID GLAND



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DISEASES

OF THE

THYROID GLAND

PART I.

MYXŒDEMA AND CRETINISM

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1900

PREFACE.

IN the following pages I have endeavoured to describe in a convenient form the results of the observations which have been made during the last few years on the functions of the thyroid gland, and their relation to the symptoms, pathology, and treatment of the diseases to which it is liable. As far as possible the clinical and pathological descriptions are founded on personal observations, and the illustrations have all been prepared from my own specimens and cases. It has been found convenient to divide the subject into two parts, so that in this volume the structure and functions of the thyroid gland will be considered together with the two diseases, myxœdema and cretinism, which are due to loss of those functions. Goitre, exophthalmic goitre, and other thyroidal diseases, will be described later in the second part. Nearly the whole of the first two of the Goulstonian Lectures on the Pathology of the Thyroid Gland, delivered by

me at the Royal College of Physicians in 1899, as well as some short extracts from my article on Diseases of the Thyroid Gland in Vol. IV. of the "Twentieth Century Practice of Medicine," have been incorporated in this volume.

G. R. M.

11, ELLISON PLACE, NEWCASTLE,
November, 1900.

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DISEASES OF THE THYROID GLAND.

CHAPTER I. THE STRUCTURE AND FUNCTIONS OF THE THYROID GLAND.

DEVELOPMENT AND STRUCTURE.

THE embryology and comparative anatomy of the thyroid gland furnish us with important information as to the origin of its present situation, structure, and function in man. The gland is developed in the embryo in three different parts. A median diverticulum of the hypoblast which lines the pharynx of the embryo is formed between the ventral ends of the second visceral arches, while a lateral diverticulum is developed on each side from the posterior wall of the fourth visceral cleft. In man the median portion persists for a time as a hollow vesicle from which a small canal, the thyreoglossal duct, leads to an opening on the dorsal surface of the tongue. At a later stage this vesicle becomes solid and the duct disappears, while its external opening on the surface of the tongue persists as the foramen cæcum in the adult. The two lateral diverticula fuse with the central portion, forming a mass shaped like a horseshoe encircling the

embryonic larynx. All three portions become separated from the hypoblast from which they originated and develop into a mass of branching cell-cylinders. These cell-cylinders are later divided up, by the ingrowth of connective tissue containing blood-vessels, into separate vesicles. These gradually increase in size and become hollowed out by the accumulation of the colloid substance which is secreted by the epithelial cells into the lumen of the alveolus. His has found that in some cases the thyreoglossal duct already mentioned does not become obliterated, but that it persists in the adult as the lingual duct which has been traced from the foramen cæcum as far down as the hyoid bone. In some cases the middle lobe of the gland is continued upwards as a narrow tube, the thyroid duct, as far as the hyoid bone. The late Professor Kanthack, who examined one hundred adults for these ducts, however, found neither a lingual nor a thyroid duct in any of the cases which he investigated, and in many there was not even a foramen cæcum. The important fact remains that the thyroid gland is developed primarily as an outgrowth of the pharyngeal hypoblast, and in some lower animals this connexion with the pharynx is still maintained. Andriezen directed attention to the fact that the thyroid gland is represented in ascidians by a mass of glandular tissue, and in amphioxus by a hypo-bronchial organ, which pours its secretion directly into the pharynx. In higher forms (such as fishes) the gland is embedded in the surrounding tissues, but the duct which communicates with the pharynx still remains. Thus the phylogenetic as well as the ontogenetic history clearly shows that the gland as we now find it in man is descended from a secretory gland which originally was provided with a duct through which the secretion passed into the

pharynx, just as the secretion of the salivary glands still flows into the mouth. In this we find an explanation of the fact that the activity of the thyroid secretion is not destroyed by passage through the stomach, but still can produce all its usual physiological effects when swallowed and absorbed from the alimentary canal, as it doubtless was by our remote ancestors. This mode of evolution seems to indicate that a ductless gland with an internal secretion is a higher stage of development of a duct gland with an external secretion.

The fully developed gland consists of three parts—two lateral lobes and the isthmus which unites them. The two lobes are closely applied to the sides of the larynx and trachea and extend backwards as far as the sides of the pharynx and œsophagus. At the level of the isthmus the recurrent laryngeal nerve lies in the angle between the œsophagus and the trachea, being covered externally by the lateral lobe of the gland on each side. In front the gland is covered by the sterno-hyoid, the sterno-thyroid, and omo-hyoid muscles. Laterally the lobes extend outwards in front of the common carotid arteries. Each lateral lobe is shaped somewhat like an almond, but the upper end is narrower and more pointed than the lower. The lower end lies on the fifth or sixth ring of the trachea, while the upper is generally on a level with the middle of the thyroid cartilage. The position of the isthmus varies, but it generally lies in front of the second, third, and fourth rings of the trachea. In many cases, variously estimated at from 40 to 68 per cent., the pyramid or middle lobe extends as a thin process from the isthmus or from a neighbouring part of one of the lateral lobes up to the hyoid bone to which it is attached by muscular or fibrous tissue. The gland is

firmly fixed to the larynx and trachea by fibrous tissue, so that it follows the movements of these structures which take place during deglutition. The gland when freshly removed is of a dark red-brown colour. It usually weighs from an ounce to an ounce and a half (from 30 to 50 grammes). It is relatively larger in the infant than in the adult; thus Huschke and Weibgen found that in newly born children the weight of the gland was equal to from $\frac{1}{100}$ to $\frac{1}{500}$ and in adults from $\frac{1}{1223}$ to $\frac{1}{1800}$ of the total weight of the body. The gland is as a rule somewhat larger in women than in men, though Ewald makes a contrary statement, supported by Weibgen, who gives the average weight in the male as 34.2 grammes, and in the female as 29.3 grammes. Each lobe is about two inches (50 mm.) long, an inch and a quarter (30 mm.) broad, and three quarters of an inch (18 mm.) deep. The right is generally a little larger than the left. The isthmus is about half an inch (12 mm.) broad and from a quarter to three quarters of an inch deep. The whole gland, however, is liable to considerable variations in structure, such as inequality in size between the two lobes, absence of one lobe, and absence or irregularity of the isthmus. There is a rich blood-supply from four arteries, the superior and the inferior thyroid arteries on each side, and in some cases there is a further supply by the thyroidea ima. These arteries are tortuous and very large for the size of the gland which they supply; they form many anastomoses and finally end in a network of capillaries closely surrounding each alveolus. The capillaries come into close relationship with the epithelial cells, and some capillary loops even project between them. The veins, which according to Sappey have no valves, unite to form the superior, middle, and inferior thyroid

veins, the two former of which open into the internal jugular vein, while the latter enters the innominate. The lymphatics start from the lymph spaces in the connective tissue which surrounds and unites the vesicles of the gland. They unite to form large trunks, which freely anastomose both in the substance of the gland and also upon its surface. On leaving the gland the lymphatics pass through the superior and inferior deep cervical glands to join the jugular lymphatic trunk, which on the left opens into the thoracic duct and on the right into the right lymphatic duct, each of which discharges into the venous blood-stream at the point where the innominate vein is formed by the junction of the internal jugular and subclavian veins on each side. The nerves which supply the gland come from the middle and inferior cervical sympathetic ganglia and pass into it with the blood-vessels. The nerve-branches run in close proximity to the bases of the epithelial cells, but the actual nerve-endings have not yet been described.

HISTOLOGY.

Externally the gland is invested by a firm fibrous capsule from which septa extend inwards, partially dividing it into lobules of various sizes. Still finer divisions of this connective tissue framework surround the individual follicles and support the small divisions of the blood-vessels, lymphatics, and nerves. The glandular structure consists of large numbers of closely aggregated follicles which vary in size and shape. On section they appear round, polyhedral, or flattened, and the diameter in man ranges from 0.045 mm. to 1 mm. In the great majority of the follicles there is a single

layer of cubical epithelial cells surrounding a central area filled with their secretion, the colloid substance. Some of the follicles seen in a section of the gland appear as masses of cubical cells without any central space. This appearance is in some cases due to one side of the alveolus alone being exposed in the section, in others to the alveolus not being distended with secretion. No basement membrane to the epithelium has been described. Two kinds of cells are found in the epithelium—the chief cells and the colloid cells. The chief cells are usually cylindrical, sometimes cubical, in shape. They measure from 8μ to 16μ in height and from 6μ to 8μ in breadth, while the nucleus which is round measures from 5μ to 6μ in diameter. The colloid cells are considerably shorter than the chief cells; thus Hürthle found in one specimen that while the chief cells measured from 12μ to 14μ in height the colloid cells were only from 7μ to 9μ high. The colloid cells are also distinguishable from the chief cells by the readiness with which they take up those staining fluids which also stain the colloid substance in the centre of the follicle. Intermediate types may also be observed. The colloid substance which occupies the central space of the alveolus is a yellow glairy fluid which stains uniformly in microscopical sections. Scattered through it may sometimes be seen white blood corpuscles, epithelial cells, and the remains of red blood corpuscles undergoing degenerative changes. The general appearance of the gland is shown in Figs. 1 and 2, which were taken from transverse sections through the lateral lobe of the thyroid gland of a bonnet monkey. These and the other micro-photographs which will be shown later have been kindly prepared from my specimens by Dr. R. A.

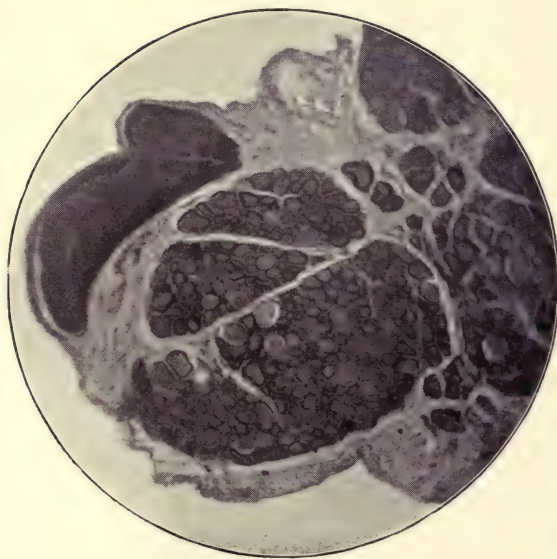


FIG. 1.—TRANSVERSE SECTION OF THYROID GLAND OF BONNET MONKEY, SHOWING STRUCTURE AND CLOSE ATTACHMENT OF PARATHYROID GLAND.



FIG. 2.—TRANSVERSE SECTION OF THYROID AND PARATHYROID GLANDS OF MONKEY, SHOWING ONE PORTION OF PARATHYROID AT LOWER EDGE OF SECTION, AND ANOTHER KITE-SHAPED PORTION JUST TO THE LEFT OF THE CENTRE OF THE SECTION. (LOW POWER.)

Bolam. These illustrations also show how closely in this animal the parathyroid is attached to the thyroid gland, in which it may be even partly embedded, as in Fig. 2—an association to which I shall refer more fully in dealing with the functions of the gland.

FORMATION AND ABSORPTION OF THYROID SECRETION.

The colloid substance is the secretion of the epithelial cells which line the alveoli. Hürthle has shown, by observations made on normal glands and on portions of glands in which increased secretory activity had been stimulated, either by removal of the greater part of the gland or by ligature of the bile-duct so as to cause absorption of bile-products into the blood, that the secretion may be formed by the epithelial cells in two ways. The colloid may be either formed in droplets in the cells and then gradually extruded into the lumen of the alveolus, or whole cells may break down and be discharged into the colloid substance, a part of which they thus help to form. In the first method the same cell continues to secrete, while in the second its place is taken by one of the reserve cells. It is doubtful if both these methods obtain during normal secretion, the first being probably the usual manner in which secretion takes place. The large amount of secretion which is found in many alveoli indicates that under ordinary circumstances it is not discharged as soon as it is formed, but that the central portion of the alveolus serves as a reservoir where the secretion is stored for a time before it finally escapes from the gland.

As the thyroid is a ductless gland, it is clear that the secretion can only escape by the lymphatics or by the veins.

The evidence which we possess shows that the former is the usual path, for it was shown by King and by Horsley that when pressure was applied to the gland the colloid could be squeezed from the acini into the interacinous lymphatic spaces, where it could be seen with the microscope. Biondi and Hürthle have found that this escape of the secretion from the alveolus may occur in two ways. The wall of the alveolus, not necessarily as the result of distension, becomes thinned out at one point and finally ruptures, allowing the colloid to escape directly into the lymphatic space outside, while the empty follicle collapses and forms the starting-point for a new one. Hürthle has found that the secretion can also pass out from the alveolus without rupture of the wall. He injected Berlin blue into the lymphatic spaces of the gland, using an intermittent pressure, and found that it passed on into the interior of the alveoli through minute intercellular channels in which it could be seen. He also found that when the secretory activity was stimulated the colloid itself could be seen lying in these intercellular channels continuous with the colloid in the alveolus at one end and with that filling the lymph spaces at the other, proving that it was passing from the former position to the latter. By one or other of these methods, then, the secretion flows into and mingles with the lymph which bathes the intervalveolar spaces of the gland, and with it flows along the path already described to be discharged into the blood-stream in the innominate vein and so distributed to all parts of the body. No doubt as in other glands the activity of the secretion varies according to circumstances; of these, however, we possess but little information. Stimulation of the laryngeal nerves or of the sympathetic with the faradaic current produces no

change indicative of increased secretion. Pilocarpin produces a marked increase in the secretion of the colloid as shown by Wyss, and Schäfer found that the changes produced in the cells were similar to those which occur in other secretory glands under the stimulating influence of this drug. As already mentioned, the presence of an excess of bile constituents in the blood after ligature of the bile-duct also stimulates thyroidal secretion. Removal of the greater part of the gland was also shown by Hürthle to serve as a stimulus to more active secretion in the remaining portion.

COMPOSITION OF THYROID SECRETION.

At one time the thyroid gland was considered to be an excretory rather than a secretory gland, and the excretion a mucinoid substance the retention of which led to an accumulation of mucin in the body and the production of the subcutaneous swelling in myxœdema. Further investigation has shown that the colloid substance is a true secretion which does not contain mucin. Our knowledge of the actual composition of this secretion is by no means complete, but several important constituents have now been separated from it. Most of those who have examined the composition of the secretion have considered the proteids to be the important and active constituents of it. Notkin regards thyreoproteid, a substance which he isolated from the gland, as an active constituent which behaves like an enzyme. Gourlay found that a nucleoproteid was the only proteid to be obtained from the thyroid in any quantity and that it contained phosphorus, which by Morkutun's analysis has been shown to amount to 0.32 per cent. Baumann and Roos made the important

discovery that the colloid substance contains iodine in an organic combination with proteid which they named "thyroidin." This substance contains 9.3 per cent. of iodine and 0.56 per cent. of phosphorus. Hutchison has found that two proteids are contained in the gland, a nucleo-albumin which is contained in the epithelial cells and a colloid material which fills the acini. The formed secretion of the gland is split up by gastric digestion into two parts, one of which is proteid, contains only a small amount of iodine, and has but slight physiological action, the other of which is non-proteid, contains more iodine and all the phosphorus of the original colloid, and is more active in removing symptoms due to loss of thyroid secretion than the proteid portion. S. Fraenkel obtained a crystalline substance with the formula $C_6H_{11}N_3O_5$ from the gland which he named "thyreo-antitoxin": there is, however, no satisfactory evidence to show that this body is endowed with active properties.

It is evident from these observations that the secretion is a complex body, and we cannot as yet say whether its remarkable properties depend on one or, as is more probable, several constituents. Be this as it may, we shall now consider what functions are fulfilled by the secretion as a whole, for that is the form in which it mingles with the blood and is thereby conveyed to the tissues.

THE RESULTS OF LOSS OF THE SECRETION IN ANIMALS.

A large amount of valuable information as to the properties and functions of this secretion has been obtained by observing what occurs when it is no longer present in the blood. This state of affairs is easily brought about





FIG. 3.—RABBIT, ELEVEN MONTHS AFTER THYROIDECTOMY, SHOWING
BALD PATCHES ON THE EAR.

by removal of the gland from an animal. Owing to the superficial position of the gland in the neck, this operation can easily be performed so as to entail no other secondary result than the loss of thyroid secretion forthwith, provided only that the parathyroid glands are not attached to the gland and removed with it, in which event the effects observed are the results of thyroidectomy *plus* parathyroidectomy. In man the effects of failure of the normal supply of thyroid secretion are seen in primary myxœdema as the result of disease, and in secondary myxœdema as the result of removal of the gland by operation for goitre. It has been shown that, although no effects have been observed in fishes, in lizards and snakes thyroidectomy is followed by loss of strength and activity, ending in death in the course of a few weeks. In rabbits the different results obtained by various observers were difficult to explain until it was shown by Gley that removal of the parathyroid glands along with the thyroid gland produced different effects from the removal of the thyroid alone. The double operation was followed by acute symptoms, the most important of which were muscular tremors commencing in the masseter muscles, clonic and often tetanic contractions of the voluntary muscles, paralysis of the extensors of the fore feet followed by that of the hind limbs, difficult and often rapid respiration, salivation, dilatation of the pupils, and rise in temperature. Removal of the thyroid gland alone was followed by no such immediate effects.

My own observations show that, although the immediate effects of thyroidectomy in the rabbit are very slight, after a long interval a chronic cachexia develops closely resembling myxœdema in man. Thus in two rabbits which were kept for a long time under observation after the thyroid

gland had been removed there was an early development of hebetude and loss of appetite. No further change was noticed until an interval of eleven months in one case and twelve months in the other had elapsed after the operation. After this, in addition to the hebetude already mentioned, swelling of the subcutaneous tissues, dryness of the skin, loss of hair, and subnormal temperature developed—an entirely different condition from that described by Gley after removal of the parathyroids as well. The illustrations show the appearance of one of these animals killed eleven months after the operation (Fig. 3) and the ears of the other killed twenty-one months after (Fig. 4). The ears were very dry, rough, and cold to the touch, though they flushed readily when handled. The edges of the ears were dry and cracked to a depth of a quarter of an inch. In many places this dried margin had broken off, leaving an irregular outline to the ear. In a third rabbit which was kept for twenty-seven months after thyroidectomy no symptoms appeared. When the animal was killed the reason of this was found to be that some of the glandular tissue had unintentionally been left at the time of the operation and had undergone compensatory hypertrophy. The total amount of thyroid tissue found weighed only 0.07 gramme or about one-third of the weight of the gland of a normal rabbit, but it had been sufficient to maintain an adequate supply of secretion for more than two years. Dogs and cats both develop a rapidly fatal cachexia after thyroidectomy. More than forty years ago Schiff showed that dogs did not long survive the operation, and in 1884 he found that fifty-nine out of sixty dogs rapidly succumbed after total extirpation of the gland. In dogs the total duration of the symptoms induced by the operation may vary from



FIG. 4.—EARS OF RABBIT WITH CHRONIC MYXEDEMA TWENTY-ONE MONTHS AFTER THYROIDECTOMY.

a few days to five weeks, but it rarely exceeds the latter period. Soon after the operation the animal becomes dull and listless and loses its appetite. These symptoms are followed by fibrillary twitchings in the muscles and clonic convulsions of the trunk and limbs, during which the animal lies on its side with the head thrown back and the limbs extended. There is great dyspnoea during these attacks, and the animal is in a half-comatose condition which becomes complete before death. There is a general diminution of muscular power and in many cases rapid emaciation. There is a slight rise of the temperature at first, which becomes subnormal before death. The red corpuscles are diminished and the white are increased in number. Very similar symptoms occur in cats. The observations of Vessale and Generali on cats and dogs, of Edmunds on dogs, and of Welsh on cats show that if the parathyroid glands are excised without the thyroid gland very similar acute symptoms occur to those observed when the thyroid and parathyroids are removed together. These symptoms are tremors, slow and unstable gait, emaciation, and weakness, all of which previously were regarded as being due to the loss of the thyroid alone.

Only a few experiments have been made on ruminants. In one a striking result was obtained by Horsley, who removed the whole of the thyroid gland from a sheep on October 3rd, 1885. No marked change was observed in the condition of the animal until May 1887, when it was shorn. Just afterwards the weather became cold, and the symptoms of acute cachexia, loss of appetite, spasms, paralysis, coma, anaesthesia, tetanoid contracture, and subnormal temperature rapidly developed and were followed by death five hundred and sixty-nine days after

the operation. The urine was found to contain an abundance of mucin, and mucinous degeneration of the ground substance of the subcutaneous tissues was described by Halliburton, as much as 0.9 per cent. of mucin being found in the connective tissues of the anterior triangle of the neck. In one donkey thyroidectomy was performed by Horsley on August 25th, 1885. At first the animal emaciated and the temperature became subnormal. After two months these symptoms disappeared, and no further change was observed till March 1886, when the weather became very cold, and anorexia, tremors, and subnormal temperature developed, followed by death a week later, two hundred and five days after the operation. These two experiments afford a good illustration of the influence of cold in precipitating the onset of the acute symptoms previously warded off by warmth.

The most important results of all have been obtained in monkeys which have been employed by Munk, Horsley, and myself. In the bonnet monkey (*macacus sinicus*), which I have used with one exception in all my experiments, a parathyroid gland lies in close connexion with or actually embedded in each lobe of the thyroid gland, as is shown in Figs. 1 and 2. As a result of this, when the thyroid gland is removed the parathyroids are removed along with it. It would be difficult to remove the one without the other, for distinctly as the parathyroid can be seen in a transverse section it is much more difficult to see it during life while the gland is *in situ*. In two recent experiments I was unable to detect, even with a lens, the parathyroids on either side and to remove them without the thyroid gland; they were, however, easily seen in transverse sections of the lateral lobes after removal of the whole gland. It is therefore important to bear in

mind that thyroidectomy in this monkey involves removal of the parathyroids as well, so that the symptoms which occur afterwards are not solely due to loss of thyroid secretion, but in part are due to loss of the parathyroids as well.

I have removed the whole or a part of the thyroid gland in nine bonnet monkeys and in one rhesus monkey. In four of the former the symptoms were allowed to develop with the object of testing the influence of various preparations of the thyroid gland upon them. Some symptoms also occurred in the others, but these four form the basis for the description of the symptoms which result from the operation. These symptoms have been very carefully described by Horsley, but they have such an important bearing upon the whole subject that I shall briefly describe what I was able to observe in my own experiments. The gland is readily removed in the following manner, when the animal is fully under the influence of ether. The skin of the front of the neck is shaved and carefully washed with one in one thousand solution of perchloride of mercury. A median longitudinal incision is made through the skin overlying the thyroid and cricoid cartilages and upper part of the trachea. On separating the muscles and exposing the upper part of the trachea the isthmus comes into view. Each lobe is then gently separated from the surrounding structures, and while the gland is held by one pair of forceps the blood-vessels are torn out of it at the point of entrance by another pair. The loss of blood is trifling and no ligatures are required. The usual antiseptic methods are adopted and the muscles are united by a couple of sutures. The skin is brought together with horsehair sutures set very close. The wound is dressed with carbolic gauze or some antiseptic wool and collodion, and it heals rapidly by

first intention. After the operation the animals have been kept in a room the temperature of which ranged between 60° and 70° F. In about five days the symptoms first begin to develop, the early symptoms being entirely nervous. One of the first to appear is a fine regular tremor which is most easily seen in the upper limbs, but which is also plainly visible in the lower limbs as well when the animal is held with the feet unsupported. Along with the tremor there is a marked change in the whole demeanour, which is the more noticeable owing to the naturally lively disposition and active habits of the healthy monkey. There is progressive apathy with loss of natural curiosity and interest in surrounding objects, while the temper is irritable, interference being resented. There is loss of activity, as the animal sits still in one place on a perch or on the floor of the cage for long periods without moving; and there is increasing loss of muscular power, as climbing is done more slowly and evidently with greater effort as the symptoms advance. The attitude assumed is characteristic: the head is bent, the trunk is curved forwards, and the knees are drawn up so that the chin rests upon them, the joints of all four limbs being in a position of flexion. This attitude is well shown in Figs. 5 and 6, taken from one of my animals. Contractures owing to tonic spasm of the flexor muscles frequently occur; in fact, this attitude is, I believe, partly a result of these contractures, as the limbs are often found to be rigid when it is adopted. Clonic contractions of the muscles are common. There may be a single contraction of a group of flexor muscles or a series of three or four may involve all the flexors of one arm, increasing in intensity until a position of extreme flexion at all the



FIG. 5.—MONKEY WITH MYXEDEMA
AFTER THYROIDECTOMY.



FIG. 6.—MONKEY WITH MYXEDEMA
AFTER THYROIDECTOMY.



joints is reached, after which relaxation takes place until another series occurs. Irregular fibrillary contractions of the superficial muscles are often visible through the skin. In consequence of these symptoms the gait is stiff and unsteady, and when the contracture is excessive the animal is obliged to walk on the heels owing to the tonic spasm of the flexors of the ankle raising the toes and sole of the foot from the ground. There is a marked tendency to fall over backwards, so that if a banana is held over the animal's head it loses its balance in looking upwards at it and falls over backwards, and a very slight push when the animal is sitting has a similar effect. True epileptic fits of greater or less intensity may occur. There may be a sudden loss of consciousness, so that if the monkey is on the perch at the time it falls to the ground. In one case I observed several epileptic fits in succession in which there was loss of consciousness, tonic spasm of the flexor muscles of the limbs, with risus sardonicus, followed by clonic contractions and micturition. In one fit there were in addition double internal strabismus with retraction of the eyelids and conjugate deviation to the left. Retraction of the head and salivation were also observed. I have seen a temporary inability to use the arms owing to spastic rigidity limiting the movement, but not actual paralysis as described by Horsley, who twice observed a complete temporary hemiplegia. The temperature at first is raised and irregular, but it soon becomes subnormal. Thus in one experiment the rectal temperature, which is usually 100° F. in this monkey, was only twice below normal during the first week following the operation, as it otherwise ranged between 100° and 102°. During the second week it only once rose to the normal level, being otherwise between

98° and 99·6°, while in the third week it varied between 97·6° and 100°, except on two evenings when it rose to 101° and 102·4°. In one experiment I found the temperature as low as 80° four days before death.

During the second and third weeks the myxœdematous swelling becomes distinct and, as in man, is most apparent in the face. Both upper and lower eyelids become swollen, and with this there is sometimes transverse wrinkling of the forehead. Both lips are also swollen by the elastic œdema. The appearance of the face is shown clearly in Figs. 5 and 7, which were taken from two different monkeys. The skin, more especially of the ears, becomes dry and rough, and the hair may be shed. Examination of the blood shows that the red corpuscles are diminished and the white increased in number. The average duration of life was found by Horsley to be twenty-four days; but he showed that when the temperature of the air in the cage was maintained at 90° the average duration of life was increased to one hundred and twenty-five days while the symptoms ran a more chronic course, like those of cretinism in man. Without giving any further details of this interesting condition its resemblance to primary myxœdema in man is remarkable. The course of the symptoms is much more acute than in man, partly because the supply of thyroid secretion is cut off suddenly by the operation, while in primary myxœdema the supply only gradually fails as the disease of the gland advances. In both conditions we have the same progressive loss of mental and bodily activity, subnormal temperature, elastic subcutaneous œdema, dry skin, and loss of hair. In the monkey we have, however, acute nervous symptoms which do not occur in primary



FIG. 7.—MONKEY AFTER THYROIDECTOMY, SHOWING SWELLING OF EYELIDS AND LIPS.

myxœdema, though some have been observed after thyroidectomy in man. I would suggest, however, from the results of removing the parathyroid glands in rabbits and other animals, that these symptoms are in part due to the loss of the parathyroids which, as we have seen, are removed along with the thyroid. This view receives further support from the fact, which will be considered later, that these acute nervous symptoms are not readily controlled by treatment with thyroid extract as might be expected were they purely thyroidal in origin. The close anatomical association of the parathyroid with the thyroid renders the removal of the former without the latter, or *vice versa*, very difficult in this animal. Under these circumstances we can remove both together and afterwards give thyroid extract to prevent the onset of symptoms from loss of thyroid secretion. The symptoms which then occur, as I hope to show, are nervous in origin and are due, I believe, to the loss of the parathyroids.

RESULTS OF LOSS OF THYROID SECRETION IN THE YOUNG.

So far we have considered only the results of athyroidism in adult animals; but thyroid secretion plays such an important part in the metabolism of normal growth of the young that it is necessary to consider the results of its loss in young animals and children, when in addition to other symptoms we find arrest of development. Hofmeister found in young rabbits from five to sixteen weeks old that thyroidectomy was followed by arrest of growth of the bones, and especially of the long bones. The skin became rough, the hair was shed, and the abdomen swelled. Von Eiselsberg removed the

thyroid gland from two male lambs eight days old and kept a third similar lamb as a control. So marked was the arrest in growth that seven months later when the control lamb weighed 35 kilogrammes the two others only weighed 14 and 10 kilogrammes each. The two together thus weighed little more than two-thirds as much as the normal animal. The lesser lamb had a small head with rudimentary horns and subnormal temperature. These experiments show how essential a normal supply of thyroid secretion is to natural growth in young animals. Of special interest in this connexion is the remarkable case recorded by Bruns, in which Sick removed an entire goitre from a boy ten years of age. Eighteen years afterwards Bruns examined the patient and found that bodily development had been arrested from the time of the operation. The expression of the face was idiotic, and there was well-marked swelling of the subcutaneous tissues, especially of the eyelids and lips. The skin was dry and the hair was scanty. The mental capacity was even less than that of an average boy of ten years of age. The speech was slow and he could do no work. In short, the case was one of advanced secondary cretinism readily explained by the fact that neither before nor after death could any trace of thyroidal tissue be found.

PHYSIOLOGICAL CHEMISTRY OF ATHYROIDISM.

A chemical examination of the tissues of several animals after removal of the thyroid gland has been made by Halliburton. In a pig and also in a donkey no excess of mucin was found. In the case of the sheep already mentioned the urine contained an abundance of mucin,

and the connective tissues of the anterior triangle of the neck 0·9 per cent., a considerable increase in the normal amount. In monkeys the percentage of mucin in the tissues is distinctly increased after thyroidectomy. A fact of special interest is the increase of mucin in the salivary glands, and especially the presence of mucin in the parotid gland, which normally does not contain any at all. Mucin was also found in increasing quantities in the blood as the myxœdematous condition developed. In some cases the blood clots very slowly, a well-marked buffy coat being formed.

RENEWAL OF THYROID SECRETION.

(a) *By grafting.*—The various results of athyroidism which we have just considered show that a sufficient supply of thyroid secretion is essential for the completion of the chemical changes in the cell which constitute normal metabolism and which, as might be expected, are even more important during the period of growth than in the adult. When the supply of the secretion is renewed, by means we shall now consider, metabolism is once more completed in a normal manner, the central nervous system and other tissues return to their natural condition, and in cretins the metabolism is so markedly reawakened that general growth, which may have been arrested for ten or even twenty years, again progresses, sometimes with surprising rapidity. The maintenance of a supply of thyroid secretion by artificial means, when the natural source has failed, is thus a question of great practical importance. The experiments of Schiff and von Eiselsberg showed that a portion of a thyroid gland, which had been successfully transplanted into the subcutaneous tissues of a dog or cat,

was able to maintain a sufficient supply of secretion, after removal of the animal's own gland from the neck, to avert the acute symptoms of athyroidism which usually follow this operation. A great advance was made by Victor Horsley, who suggested that a similar procedure should be adopted in man to arrest the inevitable progress of myxœdema to a fatal termination. This method of treatment was carried out with good results by Bircher and by Bettencourt and Serrano, as a marked improvement in the symptoms followed the operation. Unfortunately the grafted gland does not appear to be able to maintain its independent existence for long, as after a time its function ceases and the symptoms return. In only one case has the improvement been manifested for more than a few months. This was in a case of myxœdema with melancholia recorded by MacPherson, in which all the symptoms disappeared after the operation and had not returned three years later.

(b) *By thyroid extract.*—The immediate improvement observed by Bettencourt and Serrano after grafting was attributed by them to absorption of the juice of the transplanted gland by the tissues of the patient. It then occurred to me that a much simpler method of maintaining the necessary supply of thyroid secretion would be the continued internal administration of the secretion itself. It has long been good practice to supply any deficiency in the secretion of the glands of the stomach by means of a glycerine extract of the peptic glands—an acid glycerine of pepsin. I therefore prepared a glycerine extract from the healthy thyroid gland of the sheep as a convenient form in which to give the secretion. It is not necessary to describe the actual method of preparation or composition of this thyroid extract, as the original preparation

has now been included in the New Pharmacopœia under the name of "liquor thyroidei." As the secretion normally passes into the blood mixed with the lymph, I decided, in testing the efficiency of the extract, to inject it beneath the skin so that it might be absorbed by the lymphatics and so enter the blood as nearly as possible under normal conditions. This method was used at first both in man and in animals, and by it the efficiency of the remedy was first proved. It was afterwards shown independently by Howitz, E. L. Fox, and Hector Mackenzie that the extract was equally efficient when given by the mouth, so that this simpler method has since been employed both in animals and in man. The results of the treatment of myxœdema in man by thyroid extract will be described in the next chapter.

The treatment of monkeys after thyroidectomy by thyroid extract has yielded some interesting results which help us to distinguish between the symptoms due to loss of the parathyroid from those due to loss of the thyroid when both these glands are removed at the same time. The following is a brief summary of the results I have obtained :—

1. A male bonnet monkey. The thyroid gland was removed in the usual manner. No symptoms appeared during the first week after the operation. At the beginning of the second week there was a fine tremor of the arms and hands. Examination of the blood showed a slight diminution of the number of both red and white blood corpuscles. During this second week there was diminution of activity, increase of the tremors, and there were occasional clonic contractions of the muscles of the arm and forearm. A slight swelling of the upper and lower eyelids appeared. In the fourth week there was marked inactivity, the

characteristic attitude was adopted, and the tremors were well marked. There was distinct myxœdematous swelling of the eyelids and lips. The red corpuscles were diminished and the white increased in number (*v.* Fig. 9). The temperature showed marked daily variations and was subnormal on three mornings (*v.* Fig. 8). On the twenty-sixth day treatment was commenced by subcutaneous injection of thyroid extract and continued till the forty-fourth day, twenty minims in all being injected during this period.

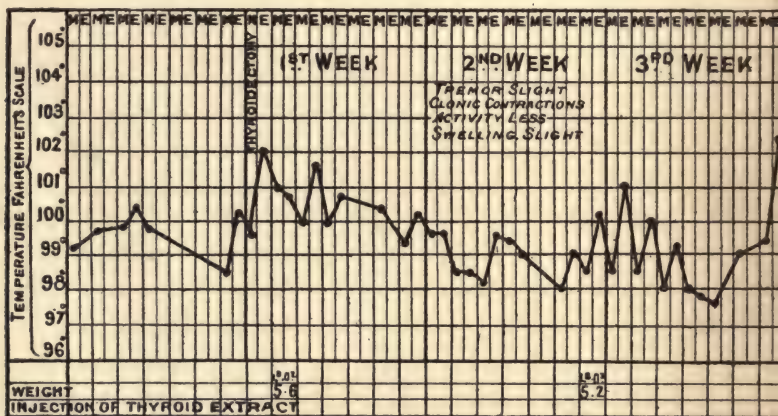
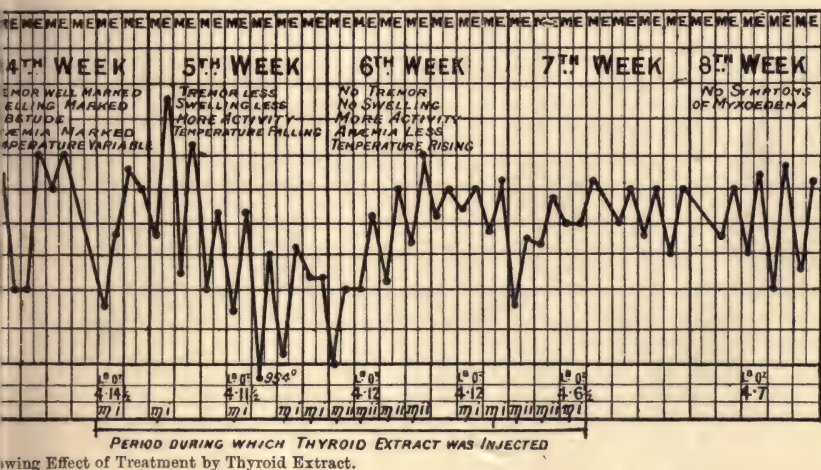


Fig. 8.—Temperature Chart of Monkey after Thyroidectomy,

As a result of this treatment during the fifth week the tremors, swelling, and anæmia all diminished and there was more activity. The morning temperature still continued to fall and was only 95.4° F. on the twenty-second day. The following day the animal had an epileptic fit, followed by an increase of the tremors and fibrillary muscular contractions and of the spastic rigidity of the flexors of the limbs, which lasted for some hours. After this the improvement steadily continued till, at the end of the seventh week, all the symptoms had disappeared

and, with the exception of a slight loss of weight, the monkey was as well as before the operation. The treatment was discontinued and the symptoms returned again much in the same manner as they had at first. Treatment was again resumed, but too late, as dysentery developed in addition to the myxœdematous symptoms and the animal died thirteen weeks after the operation. Figs. 5 and 6 show this animal after the return of the symptoms.



Showing Effect of Treatment by Thyroid Extract.

2. A male bonnet monkey. In this case the symptoms first began two days after thyroidectomy and were well marked by the fourteenth day, when treatment was commenced by injections of a solution of the alcoholic precipitate of thyroid extract in glycerine and water. The symptoms had disappeared by the twenty-sixth day. The symptoms again returned, and although improvement followed the use of thyroid extract death occurred after several severe convulsions on the sixty-ninth day.

3. In this experiment the symptoms commenced as

early as the first day after thyroidectomy. Treatment was commenced on the fifth day by injections of a solution of a nucleo-albumin prepared from fresh thyroid glands by Halliburton's method in a 2 per cent. solution of sodium carbonate. There was some temporary improvement in the symptoms, but they returned in spite of continued treatment, and death took place on the twelfth day. This experiment, however, is of doubtful value, as Hutchison has since maintained that a solution thus prepared would not contain the active secretion of the gland.

In these three experiments, though the actual presence of the parathyroid glands in the thyroid was not proved by microscopical examination, there can be little doubt that they were removed with it. In the two following experiments the animals were treated with thyroid extract for some time before, as well as after, the removal of the thyroid gland along with the parathyroids, as ascertained by microscopical examination.

4. A small male bonnet monkey was given one minim of thyroid extract by the mouth *per diem* for forty-four days and then three minims daily for the next thirty-one days, when the thyroid and the parathyroid glands were removed. The same dose of three minims was continued after the operation. No symptoms at all developed till the forty-second day after the operation. On this day it was noticed that on climbing down from the perch the monkey fell part of the way on to the floor of the cage and was unable to climb up again. It then showed general fibrillary twitching of the muscles in all parts of the body. The arms were rigid owing to spasm of the flexor muscles, which could be overcome without much difficulty, but returned at once. The legs also were flexed

at all the joints except the ankle-joints, which were extended. There was no subcutaneous swelling of the face or elsewhere. The rectal temperature was 100.6° F. A dose of six minims of liquor thyroidei was given, but the animal became worse and died the same day.

5. A small male bonnet monkey was given one minim of thyroid extract by the mouth for forty-four days; the

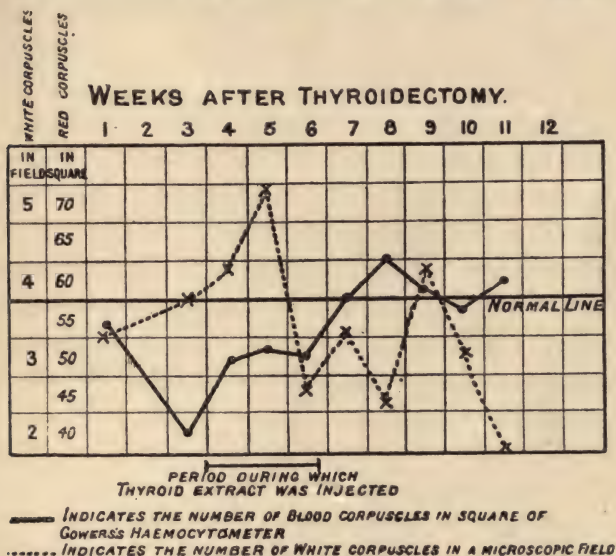


Fig. 9.—Blood Chart of Monkey after Thyroidectomy, showing Effect of Treatment by Thyroid Extract.

daily dose was then increased to three minims for the next forty-two days, when the thyroid gland was removed with the parathyroid glands. The dose of thyroid extract was continued as before. On the eleventh day after the operation there was some loss of activity and the lower eyelids were slightly swollen. After this there was progressive loss of strength and activity, and the eyelids and lips became more swollen. Spastic rigidity of the limbs developed, and on the nineteenth day after the

operation the animal was found lying dead at the bottom of the cage. The swelling of the face was largely due to the presence of a fluid œdema which escaped when the skin was incised.

It is thus evident that although in some cases the symptoms which follow thyroidectomy in monkeys disappear when the loss is made good by giving thyroid extract, in others there is only an improvement and death afterwards results with acute nervous symptoms. Edmunds has also found that under similar circumstances thyroid extract produces a marked benefit but does not save the life of the animal. From these facts, and from the results of removal of the parathyroid glands in other animals, it seems most probable that the acute nervous symptoms in the monkey, such as the fibrillary twittings, the spastic rigidity, and perhaps also the tremor and convulsions, are largely due to loss of the parathyroids, while the subcutaneous swelling, dryness of skin, loss of hair, subnormal temperature, and changes in the blood are due to loss of the thyroid secretion. This conclusion receives further support from the close resemblance of the latter symptoms to those of primary myxœdema in man, which we know to be the result of disease of the thyroid gland, there being no evidence as yet to show that the parathyroids are affected in this disease. If this be the correct explanation it is not surprising that these particular symptoms are not influenced by the thyroid extract.

We may summarise the main facts which explain the functions of the thyroid gland as follows:—

1. In all cases of *primary* myxœdema and cretinism in man there is a destructive lesion of the thyroid gland. In the great majority of cases this lesion is a fibrosis

with atrophy of the glandular epithelium such as necessarily diminishes, if it does not entirely suspend, the function of the gland.

2. In all cases of *secondary* myxœdema and cretinism in man the thyroid gland has previously been removed by operation for disease.

3. A condition of myxœdema can be induced in certain of the lower animals, especially in monkeys, by removal of the thyroid gland, and not by any other operation which spares this gland.

4. In some lower animals the symptoms which are induced by thyroidectomy can be removed or relieved by the internal administration of thyroid secretion.

5. The symptoms of primary and secondary myxœdema in man can be entirely removed by the internal administration of thyroid secretion obtained from one of the lower animals, and do not return as long as the supply of the secretion is adequately maintained.

These facts, some of which will be considered more fully in dealing with myxœdema in man, conclusively prove that the function of the thyroid gland is to supply an internal secretion which passes by the veins or lymphatics into the general circulation, and is essential for the maintenance of the normal metabolism of the body, and especially for that of the central nervous and cutaneous systems in the adult and of the growing bones as well in the young.

CHAPTER II.

MYXŒDEMA.

Derivation.—*μύξα* = mucus, and *οἶδημα* = a swelling.

Synonyms.—A cretinoid state supervening in adult life in women (Gull); cachexie pachydermique (Charcot); cachexia thyroidea, cachexia strumipriva or thyreopriva (Kocher).

Description.—Myxœdema is a term now in general use for a collection of symptoms due to loss of function of the thyroid gland occurring after fifteen years of age. In primary myxœdema this loss of function, and the consequent diminution of the supply of thyroïdal secretion to the blood, is in the great majority of cases due to chronic fibrosis with atrophy of the gland. In secondary myxœdema or cachexia strumipriva the symptoms are due to removal of the gland by operation for disease. When myxœdema occurs in infancy or childhood it is known as cretinism or infantile myxœdema.

History.—The history of myxœdema is a short but very eventful one. It is only twenty-seven years since Sir William Gull first drew attention to this condition, and during this short period all our present knowledge of its symptoms, pathology, and successful treatment has been accumulated. The symptoms of myxœdema were first described by Sir William Gull in a paper "On a Cretinoid State Supervening in Adult Life in Women" read before

the Clinical Society of London in 1873, in which he expressed the opinion that the condition was allied to sporadic cretinism previously described by Dr. H. Fagge. In 1877 Dr. W. M. Ord recorded the clinical symptoms observed in five cases, the post-mortem appearances described by Prof. W. S. Greenfield in one of them, and the results of a chemical examination of the swollen skin made by Dr. Cranstoun Charles. In this paper the condition of the thyroid gland was described, with an illustration of a microscopical section showing an advanced fibrosis of the gland. As an excess of mucin was found in the œdematous skin, Dr. Ord proposed the name myxœdema, which has since then been accepted as the usual name for this condition. After this various cases were recorded, and Charcot in 1881 proposed the name "cachexie pachydermique." The following year J. L. Reverdin described a peculiar chain of symptoms which he had observed to follow total thyroidectomy for goitre. The next year a similar condition ensuing under the same circumstances was described by Kocher, and named "cachexia strumipriva," although he considered it to be the result of a chronic asphyxia, due to injuries received by the structures in the neck during the operation, and not of the actual loss of the thyroid gland. Two months later the relationship between myxœdema and cachexia strumipriva was discussed by Reverdin. Shortly after this Sir Felix Semon, being struck by the similarity of the two conditions separately described as myxœdema and cachexia strumipriva, suggested that they were identical, and that the loss of function of the thyroid gland, which occurred in both, was the common cause of the symptoms in each of them. This suggestion led to the appointment of a special committee by the Clinical Society of London

to investigate the subject thoroughly. The experimental part of this inquiry was conducted by Mr. Victor Horsley, who by experiments on monkeys and other animals conclusively showed that *cachexia strumipriva* was due to loss of function, resulting from the removal of the thyroid gland, alone. The report of this committee also contains a detailed account of the symptoms, morbid anatomy, and pathological chemistry of myxœdema, as well as the results of an inquiry into the after-effects of both partial and total removal of the diseased thyroid gland in man. As a result of this investigation the committee found that : (1) Myxœdema and *cachexia strumipriva* are identical ; (2) sporadic cretinism is myxœdema occurring in childhood ; (3) endemic cretinism is also closely allied to myxœdema : and further, that while these conditions are dependent on loss of function, due to removal or disease of the thyroid gland, the ultimate cause of this loss of function in ordinary myxœdema is not as yet explained.

As the causation of the symptoms was thus clearly ascertained, the next advances were in the direction of rational treatment. It was shown by Schiff that the usual fatal effects of thyroidectomy in dogs could be avoided by previous transplantation of another thyroid gland into the abdomen, and by Von Eiselsberg that the same held good in the case of cats, provided the graft became vascularised and so was enabled to continue its functional activity. Quite independently in 1890 Horsley suggested thyroid grafting as a method of treating myxœdema in man. This suggestion was acted upon by Bettencourt and Serrano, who noticed a marked improvement in their patient commencing directly after the operation—an improvement which they attributed to

absorption of the juice of the implanted gland. This observation led the writer early in 1891 to suggest thyroid extract as a remedy for myxœdema, the continued internal administration of which, by hypodermic injection, he was soon afterwards able to prove was followed by the disappearance of all the symptoms of the disease. The following year it was shown by Howitz of Copenhagen and by Dr. E. L. Fox and Dr. Hector Mackenzie in England that the same results could be obtained by giving the raw gland or some preparation of it by the mouth.

ETIOLOGY.

Exciting Cause.—In primary myxœdema the symptoms are due to a loss of function of the thyroid gland, which is the result of a slowly developed fibrosis. The intensity of the symptoms varies according to the degree of fibrosis and the amount of atrophy of the glandular structure. The fibrosis may be primary, occurring as the result of chronic inflammation leading by compression to a secondary atrophy of the gland-cells, or it may be simply a replacement fibrosis, secondary to a primary atrophy of the epithelial cells of the gland. If the former is the true explanation of the mode of development of the condition, we do not know the cause of the chronic inflammation any more than, if the latter is the right supposition, we know to what the atrophy of the epithelial cells is due.

In only a few exceptional cases has the destructive lesion of the thyroid gland been traced to a definite cause. Thus Kohler has recorded two cases, in one of which syphilis and in the other actinomycosis of the thyroid gland led to the development of myxœdema. Neudorfer

has recorded another case in which an adenoma of the right lobe caused the disease. In each of these cases appropriate treatment of the exciting cause was followed by recovery of the functional activity of the gland and disappearance of the myxœdema.

Predisposing Causes. *Age.*—Myxœdema may develop at any age from infancy to old age, but when it develops in childhood it presents special features and is known as cretinism. Here I propose to deal only with cases occurring after the age of fifteen, leaving cases of cretinism to be dealt with separately. The following table, compiled from 312 cases in which the age at which the symptoms were first noticed has been ascertained, shows the relative frequency of onset in each succeeding period of five years from fifteen to sixty:—

TABLE SHOWING AGE OF ONSET.

	Males.	Females.	Total.
Between 15 and 20 . . .	1	8	9
" 20 " 25 . . .	1	22	23
" 25 " 30 . . .	4	21	25
" 30 " 35 . . .	0	32	32
" 35 " 40 . . .	8	46	54
" 40 " 45 . . .	7	52	59
" 45 " 50 . . .	6	35	41
" 50 " 55 . . .	4	25	29
" 55 " 60 . . .	2	26	28
" 60 " 70 . . .	0	10	10
" 70 " 80 . . .	1	1	2
Total . . .	34	278	312

From this table it is evident that in women myxœdema may develop at any time of life from fifteen to seventy. From fifteen to forty-five there is an increasing number of cases in each succeeding period of five years, after

which the numbers diminish. More than half of the cases occur between thirty and fifty. On comparing the different periods we find that the disease develops most frequently between thirty-five and forty-five, and more frequently during the five years following the fortieth year than in the five years which precede it. Thus it is evident that between thirty-five and forty-five, and especially during the latter half of this period, a woman is more liable to myxœdema than at any other time of her life. In nearly two-thirds of the cases in men the symptoms first appeared between thirty-five and fifty, so that this is the period of life during which the disease is most likely to develop in a man.

Sex.—Myxœdema is much more often met with in women than in men. In 425 cases of which I have been able to ascertain the sex, 370 were women and only 55 men. These figures show that the disease occurs nearly seven times as frequently in women as in men.

Heredity.—In some families a distinct predisposition to diseases of the thyroid gland has been found to exist. Thus myxœdema occasionally develops in two or more members of the same family, or other forms of thyroidal disease may occur among near relations. In several instances two and even three sisters, or a brother and sister, have suffered from myxœdema. It may appear in a mother and daughter, or an aunt or cousin of the patient may be affected. Myxœdema may be present in one member of a family while another shows symptoms of exophthalmic goitre; such an association, however, is rare and may be accidental. Tuberculosis and functional diseases of the nervous system have been found to occur more frequently than other diseases among relations of myxœdematous persons. Such an association occurs in

so many families that any special predisposition from this cause must be very slight if it exists at all.

Locality.—The distribution of myxœdema is somewhat peculiar, as it appears to be decidedly more prevalent in some places than in others, the reasons for which are not as yet ascertained. Speaking generally, it is a disease of cold and temperate climates. It is rare in the tropics even among Europeans, and I know of no case which has been observed in any of the coloured races. It is more frequent in Europe than in any other continent, and more cases have been recorded in Great Britain, where the disease was first described, than in any other country. Although myxœdema occurs in all parts of England, it is more frequently seen in the north than in the south. Thus on the banks of the Tyne, in the towns of Newcastle, Gateshead, Felling, and South Shields, with an aggregate population of 368,000, within three years I either saw or received information of twenty-nine cases. In some Scotch towns the disease is rather more frequently seen, as in 1893 Dr. Bramwell stated there were some twenty-five or thirty cases of myxœdema and cretinism living in Edinburgh, and Dr. Stalker knew of at least twenty-one cases in Dundee. The disease is uncommon in France, though eleven cases were recorded by Morvan in Lower Brittany. It is rare in Germany and Norway. In Australia it is not very uncommon, and as many as nineteen cases were recorded in one number of the *Australasian Medical Gazette* in 1894. It is well known in America, but appears to be less frequently seen there than in Europe. Isolated cases have been recorded as occurring in India, Thibet, and Cape Colony.

Personal Antecedents.—Neither social position nor domestic circumstances appear to have any influence on

the development of myxœdema. In fibrosis of other organs alcohol and syphilis are often etiological factors, but they do not appear to produce the thyroidal fibrosis of myxœdema. In some cases the onset of myxœdema is preceded by a temporary attack of exophthalmic goitre. In such cases it seems as if the process of involution of the hypertrophied thyroid gland, which is a natural method of recovery in exophthalmic goitre, had proceeded too far, leading to an atrophic fibrosis of the gland with myxœdema. This question will be considered further in dealing with symptoms and pathology of exophthalmic goitre, but there is distinct evidence to show that after an attack of exophthalmic goitre a predisposition to myxœdema may remain. Excessive child-bearing seems to be another predisposing cause, as the majority of cases occur in women who have borne children. Hun and Prudden found that out of 113 cases occurring in women, 82 were married, 14 single, and in 17 information on this point could not be obtained. Of 64 of these cases, in which the size of the family was ascertained, only 4 women had borne no children, while among the remaining 60 there had been 300 births and 29 miscarriages, or an average of 5.5 pregnancies each.

Excessive uterine hæmorrhage is a frequent antecedent to myxœdema: however, it is probably an early symptom of the disease itself rather than a predisposing cause.

SYMPTOMS.

Onset.—The onset of the symptoms of myxœdema is generally so gradual that it may be difficult to fix the actual time at which the disease has first commenced. In some cases a careful inquiry will show that slight

symptoms have existed for months or even years before they have become sufficiently prominent to attract the attention of either the patient or her friends. Quite recently I have seen an example of this in a patient who was sent to me by her medical attendant for an opinion, as she was thought to be suffering from Bright's disease. She showed slight but distinct symptoms of myxœdema, some of which had apparently been present for ten years. Sometimes a facial diagnosis can be made before the patient is aware of being out of health, as in the case of a woman who brought her daughter to me at the Newcastle Infirmary for advice and whose appearance suggested that she was myxœdematous (*vide* Fig. 10). At first she stated that she felt quite well, but on further inquiry it was found that, in addition to the facial appearance, there was increased sensitiveness to cold, slight loss of memory, and subjective visual and auditory sensations—symptoms to which she herself had attached no importance. Occasionally the symptoms develop more rapidly, and become well marked in the course of a few days or weeks, so that the nature of the disease may be clearly recognised within quite a short period of the onset. This rapid development occurs more frequently in young adults than in those who have reached middle age.

During the early stages of the disease a gradually increasing langour is often felt, so that daily occupations, formerly carried on without fatigue, become a burden. Energetic persons struggle against this, but find that more time and greater effort are required than formerly to accomplish the ordinary duties of daily life. Sensitiveness to cold may be increased, and this, combined with the lassitude, leads in many cases to the adoption of an indoor life of mental and bodily inactivity. Frontal



FIG. 10.—SLIGHT EARLY CASE OF MYXEDEMA, AGED 43, WITH WRINKLING OF SKIN OF FOREHEAD, YELLOW COMPLEXION, PINK FLUSH, SWELLING OF EYELIDS, AND LOSS OF HAIR.



FIG. 11.—CASE OF SLIGHT MYXEDEMA, AGED 53, OF TEN YEARS' DURATION, ARRESTED AT AN EARLY STAGE, WITH SUBCUTANEOUS SWELLING, WRINKLING OF SKIN, YELLOWISH COMPLEXION, PINK FLUSH, AND LOSS OF HAIR.

headache is an early symptom in some cases. The gradual development of the myxœdematous swelling in the subcutaneous tissues leads to a gradual change in appearance, which is more apt to attract the attention of those who have not seen the patient for some time than of those who see her frequently. At first there is only slight general fulness of the face, most marked in the eyelids and beneath the chin. The skin may become yellowish in colour, as if sunburnt, before the swelling is at all distinct. At this stage there is generally a red flush in the centre of the cheek, the transverse wrinkling of the forehead may already be a marked feature and the skin rather dry. These changes, being accompanied by a general increase of size and weight, are sometimes wrongly attributed to ordinary obesity. In these early stages diagnosis is sometimes difficult, as many of the more marked symptoms, which we are accustomed to see when the disease is more advanced, may be entirely absent. Thus in some cases the skin may still perspire after exertion, the temperature may be normal, and there may be no excessive loss of hair, while in others dryness of the skin appears at quite an early stage. The signs of early myxœdema will, however, be further considered in discussing the diagnosis of the disease. In a certain number of cases the disease appears to become arrested at this early stage, for a longer or shorter period, as in the case already mentioned where the symptoms though slight had already been present for some ten years (*vide* Fig. 11). In most cases, however, the disease, if untreated, gradually reaches the stage of full development. The changes in appearance which take place during the progress of the disease are well illustrated by Figs. 12, 13, 14, 15, taken

at different periods, before and after treatment, from a patient who was placed under my care by Dr. James Angus. For the first two of these photographs I am indebted to my colleague, Dr. T. Oliver, under whose care the patient was during the earlier part of her illness. When the disease is fully developed the symptoms are quite characteristic and will now be considered in detail.

Solid Œdema.—The most striking symptom of myxœdema, from which the disease takes its name, is the characteristic solid œdema of the subcutaneous tissues. This swelling, which may be slight in the early stages, is a prominent feature in more advanced cases, and though present all over the body it is most apparent wherever the subcutaneous tissues are loose. Thus there may be marked swelling of the face and of the backs of the hands, and but little of the palms or scalp where the skin is more firmly fixed to the structures which lie beneath it. The swelling may somewhat resemble in appearance that caused by fluid œdema or subcutaneous fat, for each of which it is sometimes mistaken. Thus the patient shown in Fig. 16 at first sight looked like a very fat woman, and it was only on careful examination that a considerable amount of the swelling was found to be really myxœdematous. It is said that some of the fat women in side-shows are really examples of myxœdema of this type. On palpation, however, the swelling feels softer and more elastic than fat, and, unlike ordinary œdema, it does not pit on pressure nor does any fluid exude if the skin is pricked. The movements of the limbs are often impeded by the swelling round the joints, thus a difficulty is experienced in bringing the hand up to the back of the neck to fasten the collar or in stooping to lace the boots. The power of executing



FIG. 12.

M. H., FOUR YEARS AFTER THE COMMENCEMENT
OF THE SYMPTOMS OF MYXEDEMA.



FIG. 13.

M. H., ELEVEN YEARS AFTER THE ONSET
OF THE DISEASE.



FIG. 14.—M. H., ADVANCED MYXEDEMA AT COMMENCEMENT OF TREATMENT, WHEN THE DISEASE HAD LASTED FOR TWELVE YEARS.



FIG. 15.—M. H., AFTER TREATMENT FOR SEVEN MONTHS

fine movements with the fingers, such as are required in sewing, may be lost. The general solid œdema adds considerably to the weight of the body, the increase amounting to as much as one or even two stones in some cases. The most notable change produced by the swelling is in the facial appearance. The natural outlines of the face are gradually lost, while the expression becomes stolid and fixed; so great, indeed, may be the change in advanced cases that recognition by friends has sometimes proved difficult (*vide* Figs. 12 to 18). As a result of these changes many cases of myxœdema come to resemble each other to a remarkable extent. The upper and lower eyelids are swollen and the skin wrinkled, the supra-orbital fossa being often filled by the myxœdematous swelling, while the skin just below the lower lid is baggy and translucent from the swelling beneath it (Figs. 14, 17). As a result of the swelling there is frequently some drooping of the upper eyelid, which is compensated for by an instinctive elevation of the eyebrows by tonic contraction of the occipito-frontalis muscle. This contraction causes a transverse wrinkling of the forehead which is often visible in early stages and is usually a well-marked feature in advanced cases: in the former the transverse wrinkle may be interrupted in the centre by vertical wrinkles running up from the root of the nose; in the latter, however, they generally extend right across the forehead. In one of my own cases there were small deposits of golden yellow fat beneath the exposed portions of the orbital conjunctiva on each side of the cornea; this, however, is uncommon. The nose becomes thick and swollen, but there is no real increase in size in the actual structure of the nose such as is seen in acromegaly. The cheeks are full and rounded and may even be slightly pendulous, while the centre of

each is occupied by a circumscribed red flush, which varies considerably in size and intensity in different cases and may even extend across the nose. The lips are thick and are often everted as well. There is generally considerable swelling of the subcutaneous tissues just beneath the chin, and the circumference of the neck may be so much increased that a larger size of collar becomes necessary. The supra-clavicular fossæ are partly filled up by the swelling, which rarely approaches in thickness the prominent masses which are so often present in this situation in infantile myxœdema. The swelling is fairly uniform over the trunk and limbs, but is most noticeable in the hands and feet. In the hand it is most marked over the back where the skin is loose, being less distinct on the palmar surface. It obliterates the normal features of the hand, making it broad and "spade-like" in appearance. Similar changes are seen in the feet. This enlargement of the extremities may necessitate the use of gloves and boots of a larger size than usual. In advanced cases with cardiac failure the size of the feet may be still further increased by the presence of watery œdema; the amount of enlargement due to this can be roughly estimated by the readiness with which the swelling pits on pressure. The external genital organs may be swollen or of normal size.

The Thyroid Gland.—In many cases the thyroid gland cannot be felt at all, especially if there is much swelling of the subcutaneous tissues in the front of the neck. Even after the swelling has been removed by treatment it may still be difficult to determine the size of the gland. If under these circumstances the gland still cannot be felt it is most probably diminished in size. When the gland can be detected, it is in the majority of cases found to be smaller than in health. The diminution in size can perhaps



[FIG. 16.—MYXEDEMA WITH OBESITY.



FIG. 17.

MYXEDEMA IN MAN, B., AGED 44, OF TWO YEARS'
DURATION BEFORE TREATMENT.



FIG. 18.

B., AFTER SIX WEEKS' TREATMENT BY
THYROID EXTRACT.

be most easily appreciated by passing the finger up and down over the front of the trachea and the isthmus of the gland, or by making the patient swallow a mouthful of water while the finger is pressed in over the second, third, and fourth rings of the trachea, over which the isthmus usually lies. By this means, when the upper rings of the trachea can be made out, it is in many cases quite possible to determine that the isthmus is much diminished in thickness. In a few cases enlargement of the thyroid gland has been observed. I have only seen one such case myself, and in it the symptoms of myxœdema were slight and the enlargement of the gland only moderate. In a small number of cases a definite goitre has been present.

Cutaneous System. *Skin.*—The skin and its appendages are almost always affected in early cases of myxœdema, while in advanced cases they become profoundly altered. The skin gradually becomes dry and rough owing to great diminution or arrest of secretion of the sebaceous and sweat glands, and although at first it may still be moist at times it afterwards becomes constantly dry and cold. The superficial layers of the epidermis are continually being shed as a fine white powder. This is often noticed by patients wearing black stockings, who complain that when the stockings are taken off at night they look as if flour had been dusted into them. The skin of the face is often yellowish in colour, but in some cases it is white like alabaster, while the centre of each cheek is occupied by a pink flush due to dilatation of the small veins in the skin. The yellow coloration is very marked in some cases, and, combined with the pink flush in the centre of each cheek, gives a complexion not unlike that of a sunburnt country-woman with rosy cheeks who has been

accustomed to work in the fields. I have known the yellowness of the skin to be attributed to jaundice by the patient's friends, from which, however, it is readily distinguished by its limited distribution and by the absence of yellow colour from the orbital conjunctiva. The skin over the back in some advanced cases is dry and scaly and may even resemble a condition of ichthyosis. These characters are often very marked over the extensor aspect of the knees and elbows. The peculiar wrinkling of the skin which is often present on the backs of the hands and fingers is shown in Fig. 19. The skin of the palms and soles is dry and rough and not infrequently cracked. Both hands and feet feel cold to the touch. Sensible perspiration, which may still be present in early cases, gradually diminishes as the disease progresses; it finally disappears in advanced cases and may be entirely absent for several years. Insensible perspiration is also greatly diminished, only some 40 to 60 per cent. of the normal amount of water being discharged from the skin as aqueous vapour. Sebaceous secretion also gradually dries up in a similar manner. Warts and pigmented moles occur on various parts of the skin in a considerable number of cases.

Hair.—The hair of the head becomes thin and scanty in nearly all cases. In some the head is almost completely bald; the skin of the scalp then becomes dry, brown, and scaly, the superficial layer of dried epidermis being cracked from front to back and from side to side as in Fig. 14. The hair which is not shed becomes fine in texture, soft to the touch, and is sometimes curly. The hair of the face, eyebrows, eyelashes, axillæ, and pubes is often scanty or it may disappear altogether.

Nails.—The nails are often cracked, grooved, and discoloured.



FIG. 19.—SHOWING CONDITION OF SKIN AT BACK OF HANDS IN MYXEDEMA.

Teeth.—The teeth are frequently brittle and carious and in a considerable number of cases only a few remain.

Mucous Membranes.—The mucous membranes are pale and opaque and may be swollen like the skin. The mucous membrane of the lips is often swollen, dry, and purplish in colour. The dryness of the mucous membrane is most obvious in the mouth and nose. In some cases there is a flow of saliva from the mouth during sleep.

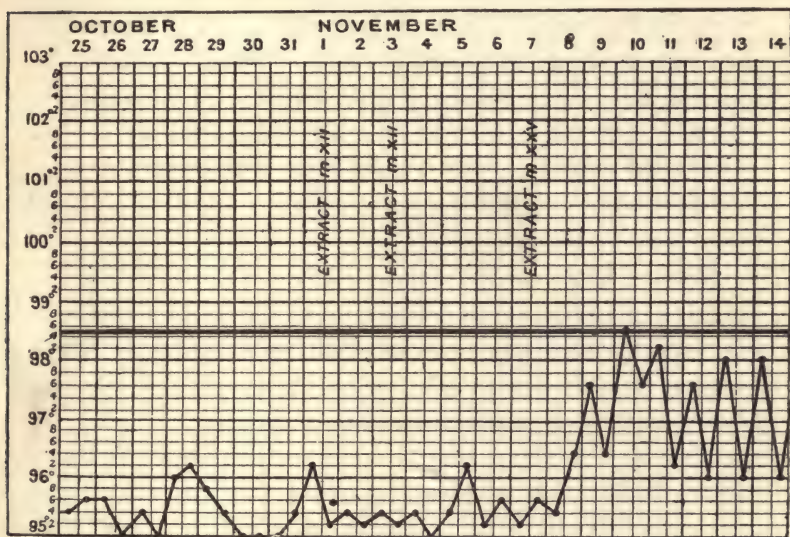


Fig. 20.—Temperature chart of case of myxœdema shown in Fig. 14, showing subnormal temperature before treatment and rise of temperature after treatment.

Temperature.—In early cases of myxœdema patients often make no complaint of feeling cold and the temperature may remain normal. In more advanced stages they generally feel the cold much more acutely than they did formerly, and complain that they can never get warm during the cold weather. In winter such patients like to spend most of the day sitting well wrapped up by a

warm fireside, and require very warm beds at night. In warm weather they feel much better. The skin, especially of the extremities, feels cold to the touch. The temperature in fully developed cases is almost continuously one, two, or three degrees below normal, as is shown in Fig. 20 in the portion of the temperature chart taken before treatment was commenced. In some cases the temperature may be only from 93° to 95° F., and cases have been observed in which it fell to 77° and even as low as 66° shortly before death. It is important to bear in mind that in such cases a rise of temperature to 98° or 99°, occurring independently of treatment by thyroid extract, is a sign of fever, equivalent to a rise to several degrees above normal in a healthy person, and may therefore indicate the onset of some febrile complication such as tuberculosis.

Nervous System.—We have already seen in the experimental myxœdema of lower animals how prominent nervous symptoms become when thyroidal secretion is no longer formed, but that some of them may be due to the loss of the parathyroids rather than to the absence of the thyroid gland alone. In the myxœdema resulting from a slowly developing thyroidal fibrosis, which we are now considering, the nervous symptoms are less acute and take a secondary position in many cases to the general symptoms which have just been described. In almost all cases, however, we find some marked functional derangement of the central nervous system which can be removed by treatment, and in a few cases of long duration signs of more serious structural changes which are permanent. The main characteristic is a general slowness in execution of all functions of the nervous system.

Mental Symptoms.—Marked intellectual changes occur in many cases in which no signs of insanity are present, and in almost every case some change in the mental condition can be detected. These changes are characterised by slowness in comprehending new subjects, in thinking and in carrying out any new project. Abnormal persistence in one line of thought or action occurs in about one-fourth of the cases, who dawdle a long time over ordinary daily duties such as dressing in the morning. The memory is usually deficient for recent events, while there may be a clear recollection of those which occurred before the commencement of the disease. The temper is usually placid and equable, though some patients are very irritable, and even those who as a rule are good-tempered are liable to occasional outbursts of irritability, if annoyed by any unusual occurrence. The fixed facial expression frequently conceals emotions which would otherwise be apparent. The alteration in personal appearance is often acutely felt, and renders many patients shy and unwilling to be seen by strangers; others, again, have a morbid dread of crossing open spaces. As a result of these tendencies, most myxœdematous persons are fond of staying at home and rarely leave the house unless obliged to do so. Drowsiness during the day is common, and sleep at night is usually sound, though in some cases it is disturbed by disagreeable dreams and sensations. Hallucinations frequently occur in advanced cases and are not at all uncommon in quite early ones; in the latter they are generally indistinct. Thus these patients often see some ill-defined object moving rapidly across the floor, like a rat or cat indistinctly seen in the dusk, without being able to state exactly what it was; or they may hear a noise as of the door opening behind

them. In the more advanced stages the hallucinations of sight and hearing may be remarkably clear and distinct: a well-known friend or an animal is seen or a familiar voice is heard. For example, one of my patients (*vide* Fig. 16) told me that her father, during the latter part of his life, had been in the habit of coming to see her in the morning before she got up. After his death she distinctly saw him on several occasions walk into the room and sit down beside her bed, and on one occasion she heard him say quite clearly, "A—— hinny, you are getting too fat."

Insanity.—Insanity occurs in a certain number of advanced cases of myxœdema which have not been treated. A few years ago such cases were to be found in many of our large asylums, but now, owing to proper treatment being adopted early, they are less frequently seen. Myxœdema may of course develop in the insane, but such cases of primary insanity must be carefully distinguished from the cases in which the insanity is secondary to the myxœdema, with which we are now dealing. In some cases the peculiar mental and intellectual changes, which have just been described as occurring in many cases of myxœdema, gradually become more profound till the patient is actually insane. Such cases may develop either acute or chronic mania, melancholia, or dementia. The natural shyness and tendency to shun observation, on account of the altered appearance, may pass into a condition of suspicion or into the delirium of suspicion. The mental weakness gradually increases, and there may be occasional outbursts of violence until finally dementia is developed, often in conjunction with great physical weakness. In some cases doubt, irritability, and exalted ideas may occur in addition, and in the late

stages convulsions ending in coma and death are not infrequent.

Motor Symptoms.—Voluntary movements are executed slowly and deliberately. The range of movement of the joints may also be limited, as already mentioned, by the swelling of the subcutaneous tissues surrounding them. The gait is consequently slow and leisurely. The speech is also slow, and the voice is often thick and monotonous, the power of singing being lost. This change in the character of the voice is, however, chiefly to be attributed to the thickness of the lips and the swelling of the tongue, uvula, and soft palate. Some write slowly, but, provided the education is good and plenty of time is allowed, clearly expressed letters of considerable length can be written. General muscular weakness is a common symptom, and in advanced cases it may be all the more marked owing to prolonged inactivity. The weakness affects chiefly the muscles of the limbs and neck; the latter may be so weak in some advanced cases that the head falls forward till the chin rests upon the sternum. Some complain that the knees occasionally give way suddenly. Actual paralysis only occurs as a complication, and contractures of the limbs, such as are seen in monkeys after thyroidectomy, rarely if ever occur in primary myxœdema. Incoördination occurs not infrequently and has in some cases been the cause of injuries in consequence of falls.

Sensory Symptoms.—Subjective sensations affecting either general or special senses are common. A feeling of coldness or chilliness, due to the subnormal temperature of the body, is most frequently complained of, especially in cold weather. Frontal and occipital headaches often occur, and neuralgic pains, or sensations of pricking,

numbness, and the like, are felt in various parts of the body. Attacks of vertigo and tinnitus are not uncommon. Tactile sensation is diminished in some cases ; in many, however, it is unaffected. Sensation to heat and cold may be unaltered or there may be an increased sensitiveness to cold. Retardation of sensory impulses has been observed in a good many cases, but the slowness in response is no doubt partly to be attributed to the hebetude of the patient.

Special Senses.—Sight is impaired in about half of the cases, but in many this impairment is due to causes unconnected with myxœdema. The committee of the Clinical Society determined that in a small proportion of cases a general diminution in acuteness of vision and watering of the eyes were to be attributed to the disease. In some cases limitation of the field of vision has been observed, and in a few, atrophy of the optic nerve, and œdema of the retina. Hearing also is diminished in some 50 per cent. of the cases. There may be deafness of one or both ears, which in the majority of the cases is to be attributed to the myxœdema. I have seen one interesting case of advanced myxœdema with Dr. Dalglish in which deafness had been almost complete but had disappeared suddenly during treatment by thyroid extract. Taste and smell are impaired in about one-third of the cases. Sexual feeling may be diminished in both sexes ; but one case has been recorded in which a man with well-marked myxœdema married and became the father of two children. Myxœdematous women rarely become pregnant.

Reflexes.—The superficial reflexes may be diminished, but they are rarely absent. The myotatic irritability, as shown by the tendon reflexes, as a rule is unaltered,

though in some cases it is diminished and in others increased. I have seen two cases—one with Dr. J. Blood of Birkenhead, and the other with my father, Dr. William Murray—in which the knee-jerks were exaggerated and there was slight ankle-clonus associated with difficulty in walking. This was evidently due to lateral sclerosis, which was probably an accidental complication rather than a result of myxœdema.

Circulatory System. *Heart.*—In a large number of cases and especially when the symptoms are slight the heart is normal. In cases of long duration, in which the symptoms of myxœdema are advanced, there may be palpitation, dyspnœa on exertion, and attacks of syncope. In a case I saw with Dr. H. Walker of Newcastle the syncopal attacks were so severe that they would probably have proved fatal if the patient had not been staying in his house at the time and a suitable treatment applied at once. As it was, this patient, after being cured of her myxœdema by thyroid extract, died in half an hour from an attack of syncope induced by stooping, when she was living in the country where no immediate medical aid was available. In such cases the heart-sounds and the cardiac impulse are feeble; the aortic second sound may be accentuated. Lesions of the aortic and mitral valves with hypertrophy and dilatation of the left ventricle occur in some cases, but are probably only accidental complications. The patient shown in Figs. 12 to 15 ultimately died from the effects of advanced mitral constriction, although no murmur was audible while she was under my observation. The weakness of the heart due to degenerative changes in its muscular wall is of special importance in connexion with the treatment of myxœdema by thyroid extract. Under this treatment the rapid

improvement in the general condition is apt to lead to undue activity before the heart is able to bear any additional strain. In addition to the case mentioned above, another of my cases, who had symptoms of cardiac degeneration, succumbed to heart failure while walking up a hill not long after the commencement of the treatment. In one such case, recorded by Dr. John Thomson, extensive fatty and fibroid degeneration of the heart was found at the post-mortem examination.

Pulse.—The pulse is as a rule less frequent than in health, regular, slow, weak, and of low tension. If either cardiac or renal disease is present the pulse will vary according to the character and gravity of the lesion. In most cases no change can be detected in the arterial wall, though atheroma and thickening of the arterial wall have been described in a few.

Blood.—There is generally a moderate degree of anæmia, as shown by the pallor of the mucous membranes. The red corpuscles are diminished in number and deficient in hæmoglobin. The number of red corpuscles in the cubic millimetre generally lies between 3,000,000 and 4,000,000 and rarely falls below the former number, while the amount of hæmoglobin varies from 60 to 70 per cent. and in a few from 40 to 60 per cent. of the normal. The red corpuscles are otherwise unaltered in appearance, though Kræpelin has described an increase in their diameter in three cases and has found the specific gravity of the blood and serum to be increased. In some cases the white corpuscles are slightly increased in number.

Hæmorrhages.—Hæmorrhage is a common symptom in myxœdema, and most frequently occurs as menorrhagia, or as excessive bleeding during parturition. In some

cases the gums bleed very readily, especially after the extraction of a tooth. Hæmorrhage may also take place from the nose, throat, or bladder, and some patients bleed freely after slight injuries such as a pin-prick.

Urine.—The urine may be quite normal, and usually is so, in the early stages of the disease. In fully developed cases it is often pale in colour with a rather low specific gravity, ranging from 1·008 to 1·018, and the amount of urea is generally diminished. In some 20 per cent. of cases of myxœdema the urine contains a small amount of albumin. In a few cases the albuminuria is due to actual disease of the kidneys, and in such the urine may contain casts as well. In the older cases there may be some fibrosis of the kidney. In the majority of these cases, however, the albuminuria is a direct result of the myxœdema, as is shown by the fact that it disappears along with the other symptoms under treatment by thyroid extract, as in one of my own cases. Albumosuria has also been observed by Fitz.

Digestive System.—The appetite is generally poor and dyspepsia is not uncommon. Constipation is frequently complained of and some patients suffer from hæmorrhoids as well. The lips share in the general swelling of the face. The teeth are generally in bad condition, being brittle, irregular, and discoloured. In cases of some duration they are often broken and carious or have disappeared entirely. The gums are pale if there is anæmia, and are frequently swollen; they may be soft, spongy, or ulcerated, and may bleed readily after slight injuries. In some cases a thick mucous discharge runs out of the mouth during sleep on to the pillow. In fully 50 per cent. of the cases the tongue is swollen, in some to a considerable degree, and in exceptional cases it may be cracked and sore. The

uvula and soft palate are not infrequently swollen, but no difficulty in swallowing as a rule is experienced.

The Generative System.—In the early stages of myxœdema menorrhagia is not uncommon, but when the disease is fully developed there is usually amenorrhœa. In some cases the amenorrhœa is present because the disease has commenced about the menopause; in others, however, it undoubtedly occurs as a result of the disease, as menstruation is re-established when the myxœdematous symptoms have been removed by treatment. Pregnancy seldom occurs after the onset of the disease as so many patients have already arrived at the menopause. Even in younger women it is rare, and when it does occur there is a tendency to post-partum hæmorrhage. In the male no special change has been noticed in sexual power, and as already mentioned one case has been recorded in which the patient married and became the father of two children while suffering from myxœdema. In both sexes the external organs of generation may be swollen, the skin covering them is dry, and the pubic hair scanty or absent, as part of the general condition of the skin and its appendages.

NATURAL COURSE, DURATION, AND TERMINATION.

The course and duration of myxœdema have been so entirely altered by the introduction of the thyroid treatment that the following remarks apply only to observations made upon cases treated by the older and merely palliative methods of treatment, in which the symptoms ran their natural course sooner or later to a fatal termination. The course of the disease is usually slow and the condition of the patient may remain stationary for several years

at a time. As will be seen from the subjoined table, myxœdema may last for twenty or even thirty years. Temporary improvement is not uncommon; thus patients are often much better in the summer or during a visit to a warm climate, but they relapse into their former condition on the return of cold weather. In a few cases the symptoms have disappeared during pregnancy, probably, as Dr. Hector Mackenzie suggested, owing to the absorption of the secretion of the thyroid gland of the fœtus by the mother. Three cases of spontaneous recovery have been recorded which are difficult to explain, unless the symptoms were due to some temporary blocking of the channels by which the secretion leaves the gland, and not to the usual condition of thyroidal fibrosis with atrophy which cannot be removed. Dr. Fraser of Paisley, who recorded one of these cases, was kind enough to inform me that no return of the symptoms of myxœdema had occurred during the succeeding ten years. In the three cases already mentioned in which the symptoms were due to syphilis, actinomycosis, and adenoma of the thyroid gland respectively, appropriate treatment of these conditions was followed by recovery of the gland and disappearance of the myxœdema. Apart from these exceptional cases the symptoms sooner or later get steadily worse and the patient dies. The following table, compiled from three hundred and twenty cases, gives the duration of the disease at death or at the time the case was recorded or treatment by thyroid extract was commenced. As many of these cases were living at the time the record was made, it will be evident that the duration as given by this table falls short in many instances of the actual full duration of the untreated disease.

TABLE SHOWING DURATION OF MYXŒDEMA.

	Males.	Females.	Total.
Less than 1 year . . .	3	16	19
At least 1 year . . .	1	22	23
" 2 years . . .	5	36	41
" 3 " " " " . . .	3	31	34
" 4 " " " " " . . .	2	28	30
" 5 " " " " " . . .	4	23	27
" 6 " " " " " . . .	4	15	19
" 7 " " " " " . . .	4	12	16
" 8 " " " " " . . .	4	13	17
" 9 " " " " " . . .	1	10	11
" 10 " " " " " . . .	1	18	19
" 11 " " " " " . . .	0	8	8
" 12 " " " " " . . .	0	12	12
" 13 " " " " " . . .	0	3	3
" 14 " " " " " . . .	0	8	8
" 15 " " " " " . . .	1	9	10
" 16 " " " " " . . .	0	3	3
" 17 " " " " " . . .	0	5	5
" 18 " " " " " . . .	1	1	2
" 20 " " " " " . . .	0	6	6
" 21 " " " " " . . .	1	1	2
" 24 " " " " " . . .	0	1	1
" 26 " " " " " . . .	0	1	1
" 30 " " " " " . . .	0	1	1
" 32 " " " " " . . .	0	1	1
" 34 " " " " " . . .	0	1	1
Total	35	285	320

Death may occur as the result of some complication such as influenza, bronchitis, pneumonia, diarrhœa, or other intercurrent disease, to which the patient, already enfeebled by the myxœdema, readily succumbs. Cardiac failure from degeneration of the heart, insanity, cerebral hæmorrhage, or fibrosis of the kidney associated with arterio-sclerosis may also be immediate causes of death. In some cases death apparently results from the general debility and exhaustion entailed by the myxœdema itself.



FIG. 21.—THYROID GLAND FROM CASE OF MYXEDEMA.

Since the introduction of the treatment by thyroid extract the disease is no longer allowed to run its natural course. By this treatment the patient can now be entirely cured of myxœdema, and will remain free from it as long as the treatment is continued, although the thyroïdal fibrosis and atrophy remain as before. My patient, who was the first case to be cured by the internal administration of thyroid extract, is still, nine years after the commencement of the treatment, alive and free from myxœdema, so that when the treatment is commenced early, before any incurable degeneration of any important organ has taken place, and is continuously kept up, there seems no reason why loss of function of the thyroid gland should of itself lead to a fatal termination or even shorten life.

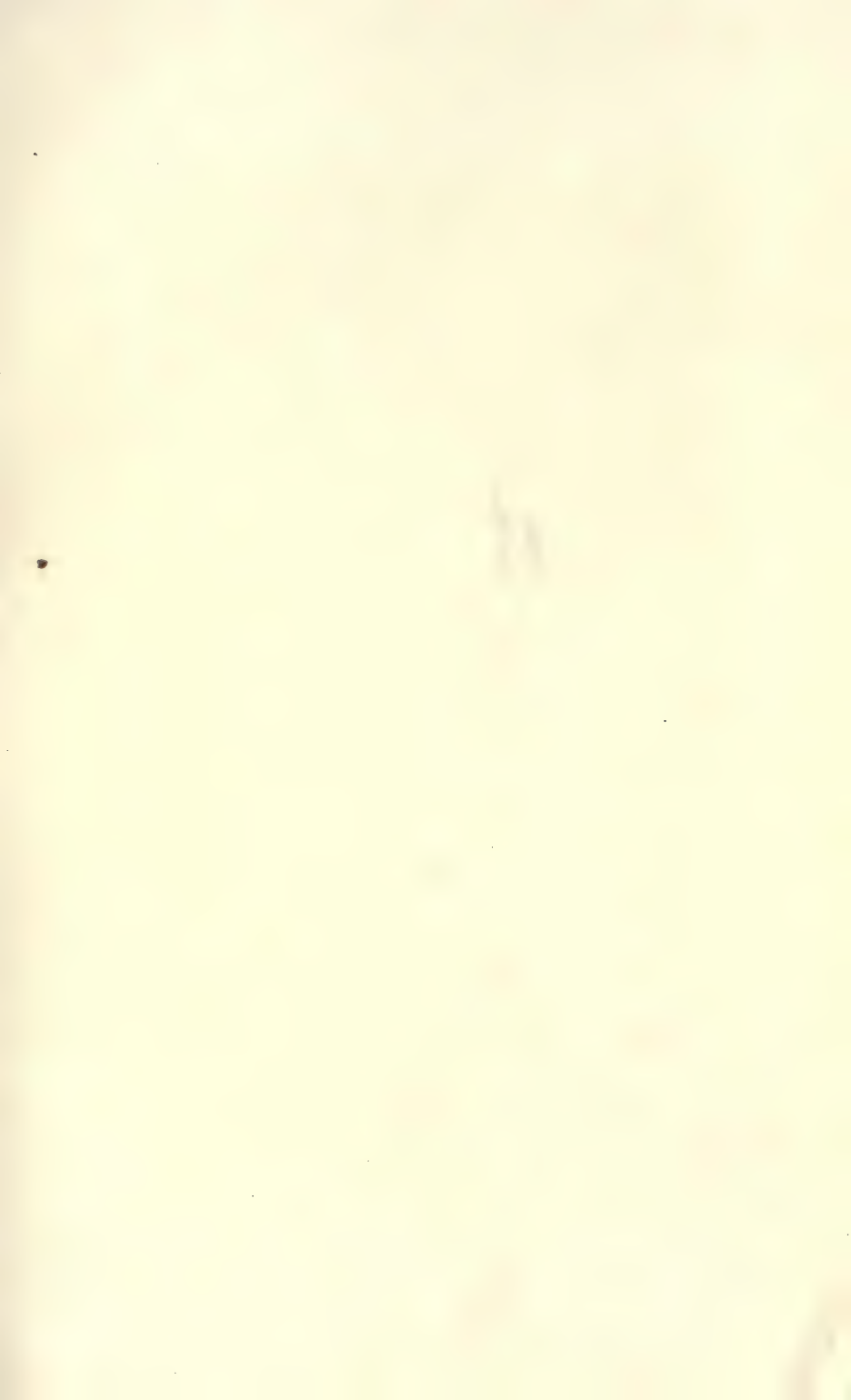
MORBID ANATOMY.

The Thyroid Gland.—In nearly all cases the thyroid gland is found to be diminished in size, often to a very considerable extent. Thus one of my specimens only weighed 4·5 grammes (67·5 grains), and another, shown in Fig. 21, only weighed 3·5 grammes (53 grains) or about one-tenth of the normal weight of the gland. In exceptional cases the gland has been found to be larger than normal. Cummins has recorded such a case, in which the enlarged lobes were found on section to be pale in colour, tough and fibrous in consistence, and to contain no normal thyroïdal tissue, showing that, although enlarged, the gland was functionally inactive. The microscopical examination shows that the usual condition of the gland is one of general fibrosis with atrophy of the secretory epithelium. Unfortunately we know very little as yet of the cause or mode of origin of thyroïdal fibrosis.

It may, according to the older views, be regarded as a chronic inflammation, a chronic interstitial thyroiditis, as a result of which new fibrous tissue is formed which by its slow contraction and constriction of the blood-vessels and alveoli leads to the destruction of the epithelial cells. On the other hand, it seems more probable that the atrophy of the glandular tissue takes place primarily as the result of the action of some toxic agent, and that the fibrosis is only a replacement fibrosis, such as occurs in the spinal cord and elsewhere after more highly organised structures have been destroyed. This problem, which is one with that of the origin of fibrosis of other glandular organs, such as the liver and kidney, does not concern us further here, for however it originates the result of the disease is a slowly progressing destruction of the gland with gradual diminution and final arrest of secretion.

In the early stages of the disease the walls of the alveoli are infiltrated with small round cells and the epithelial cells appear to be proliferating. This condition gradually advances into one of general fibrosis with thickening of the capsule, owing to an increase of the fibrous tissue in it which is continuous with that of the stroma of the gland. The walls of the arteries become thickened, especially in the middle and outer coats, and the lumen of the vessel may be considerably diminished or even occluded if the vessel is small.

The structural changes in thyroïdal fibrosis may be very extensive; thus in one specimen, for which I am indebted to Dr. Callcott of Gosforth, the whole gland was much diminished in size and pale yellow in colour. The right lobe measured one and a quarter inches in length and the left lobe one and a quarter inches, and the isthmus a quarter of an inch in width. The general



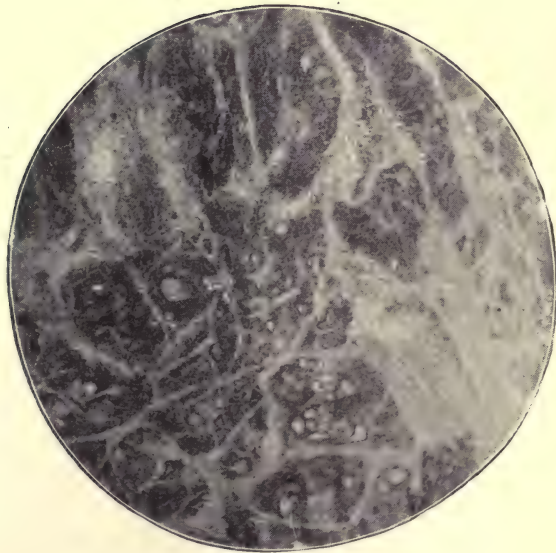


FIG. 22.

THYROIDAL FIBROSIS WITH ADVANCED ATROPHY.

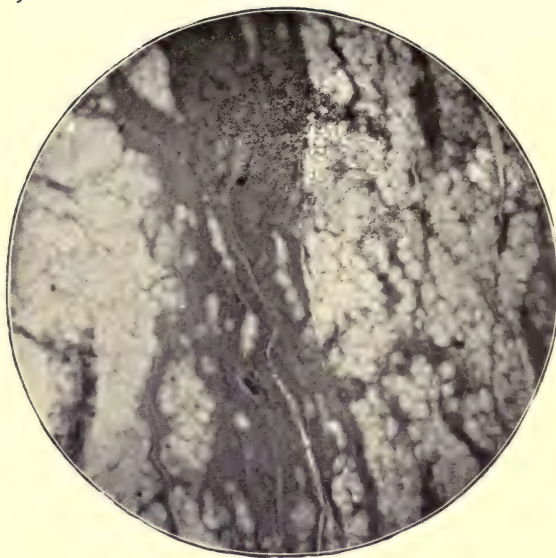


FIG. 23.

THYROIDAL FIBROSIS WITH COMPLETE ATROPHY.

appearance is shown in Fig. 21. The day after it had been removed and placed in spirit it weighed 3·52 grammes, or only about one-tenth of the normal weight. The microscopical structure is shown in Fig. 22, from which it will be seen that only a few scattered alveoli are left, and even in some of these only a few of the epithelial cells still survive. The rest of the gland is made up of richly nucleated areas of young fibrous tissue divided by wide strands of older fibrous tissue with few nuclei. In another case (*vide* Fig. 14) in which death occurred from mitral disease eighteen years after the onset of the myxœdema, for the last six of which she had been treated by thyroid extract, the gland was pale yellow in colour and weighed 4·5 grammes. The whole of the gland, as is shown in Fig. 23, was converted into fat and fibrous tissue and not a trace of the original glandular structure remained. It is therefore quite evident that very little if any secretion would be formed in the gland shown in Fig. 22, and certainly none at all in that shown in Fig. 23, in which for long there must have been complete arrest of thyroidal secretion.

The Skin and Its Appendages.—The condition here described is that which has been found in cases of myxœdema which died in the fully developed stage of the disease unrelieved by thyroid treatment. To the naked eye the skin appears thickened as in life and on section it looks translucent as if soaked in some semi-fluid substance. On microscopical examination the epithelium of the epidermis may be found to be slightly atrophied, while in the connective tissue of the corium the trabeculæ are replaced by bundles of fine fibrillæ with nuclei, and the lymphatics are dilated. In exceptional cases the interfibrillar spaces are unusually wide,

as in ordinary fluid oedema, so that the fibrillæ and nuclei are shown very clearly. The ground substance is considerably increased. Here and there in the upper part of the corium, and especially round the small blood-vessels, there are irregular collections of small round cells. In some cases the blood-vessels show thickening of the walls due to endarteritis, as Dr. Ord pointed out in his original paper, in others they appear to be normal. The cutaneous nerves are usually unaltered in structure, though in one case an overgrowth of the perineurium has been observed. In the sweat-glands the epithelium of the coiled tubules is swollen in the earlier stages, the nuclei proliferate, and the lumen of the gland becomes occluded. In the later stages the tubes are found to be surrounded by newly formed fibrous tissue. The sebaceous glands undergo similar changes, and in advanced cases only a few or possibly none of the epithelial cells of the gland may be left. In some cases the changes in the hair follicles are only slight, in others they are extensive. The hair follicles are seen to be surrounded by fibrous tissue with many nuclei, which after a time contracts, causing irregular compression and atrophy of the root-sheath; this leads to the loss of the hair, and in a later stage the follicle may be represented only by a mass of cells occupying its original situation. The same appearances are found in the skin of all parts of the body, though the changes in the hair follicles are naturally seen best where the hair is most abundant in health, as on the scalp. These alterations in the structure of the skin readily explain the absence of perspiration, the dry skin, and loss of hair, which are such constant symptoms in advanced myxœdema. Profound though these changes appear to be, it is important to remember

that, even when the disease has lasted ten or twelve years, the skin is capable of restoration to its normal condition, for under the influence of treatment the sweat-glands regain their secretory activity and new hairs are developed from the hair follicles.

Fat.—The increase in weight which is a notable feature in some cases of myxœdema is partly due to an increase in the amount of subcutaneous fat, which in nearly all cases is found to be abundant. In some the omental and subperitoneal fat is also increased in amount. Microscopically the fat cells are sometimes smaller than normal, and in one case Boyce and Beadles found vacuoles in the nuclei of nearly all the fat cells.

Hypophysis Cerebri.—The condition of the hypophysis cerebri has not been ascertained in many cases of myxœdema. In several it has been found to be enlarged, even to double the normal size. In the specimen shown in Fig. 21 the hypophysis appears to be somewhat enlarged. It measured $\frac{9}{16}$ inch transversely, $\frac{3}{8}$ inch in the antero-posterior diameter, and $\frac{1}{4}$ inch in the vertical diameter, and weighed $9\frac{1}{4}$ grains ($\cdot 6$ gramme), which, however, comes within the limits of the normal weight given by Quain as from 5 to 10 grains. The hypophysis of the case shown in Fig. 14 also weighed $9\frac{1}{4}$ grains ($\cdot 6$ gramme.) Boyce and Beadles found, in the case recorded by them, that the increase in size was due to hypertrophy of the anterior glandular portion, which on microscopical examination showed signs of unusual activity by an increase in the size of the epithelial cells lining the alveoli and the presence of colloid material in the alveoli and lymphatic spaces.

Nervous System. *Brain.*—No constant changes have as yet been found in the brain, though it is possible such

may be discovered by means of recent methods of staining. Endarteritis and periarteritis of the cerebral vessels occur as in arteries of other parts of the body. Slight hæmorrhages, general œdema, increase of fibrous tissue, and cortical atrophy have been observed in some cases. Whitwell, in one case in which there had been delusional insanity, found marked vacuolation of the nerve-cells and their nuclei in the gray matter of the motor cortex, and a distinct increase of connective tissue throughout the gray matter.

Spinal Cord.—In nearly all cases the spinal cord has been found to be normal. In one case degeneration of the anterior horns of the gray matter was found, and in another thickening of the pia mater. In one case, in which there had been a staggering gait, Dr. Ord found the septa, especially in the posterior columns of the cord, were thickened. These changes were probably accidental complications independent of the thyroidal disease.

Nerves.—As a rule no changes are found in the peripheral nerves. In a few cases a neuritis has been found, especially in one described by Boyce and Beadles in which there was perineuritis and endoneuritis of the muscle nerves.

Sympathetic Nervous System.—Of the cases in which the superior cervical ganglion was examined for the committee of the Clinical Society, fibrosis was found in five and probable interstitial changes in three. Similar changes have been described in healthy persons and in other diseases, so that little importance can be attached to them in myxœdema.

Circulatory System. Heart.—In the earlier stages of the disease the heart is usually quite healthy. In some advanced cases degenerative changes of the cardiac muscle

are found. In some cases the left ventricle is found to be hypertrophied; but in association with this there is found fibrosis of the kidneys, to which the hypertrophy is secondary. Considering how frequently symptoms of cardiac degeneration have been observed in advanced cases, a comparatively small number of post-mortem records contain any account of fatty or fibrous degeneration of the wall of the heart. Interstitial myocarditis has been found in a few cases, and fatty and fibrous degeneration occur, possibly as a late result of myocarditis. Atheroma and endarteritis of the coronary arteries are found in some cases, and they also tend to bring about degenerative changes in the muscular tissues of the heart. Scattered collections of small round cells have been found lying just beneath the visceral layer of the pericardium, in the immediate neighbourhood of the blood-vessels, by several observers. Valvular lesions are also occasionally found, as in one of my cases in which there was an advanced degree of mitral constriction though no murmur was audible during life.

Arteries.—Atheroma of the aorta and larger arteries is common, as it has been found in about half of the cases examined. It is rarely in an advanced condition. In one of my cases there were calcareous patches near the base of the aorta. Endarteritis of the smaller vessels is of frequent occurrence and may be found in all parts of the body. Some of the affected vessels may be occluded.

Kidneys.—Some renal fibrosis is frequently found; as a rule it is not intense, though it may be sufficiently advanced to lead to some destruction of the epithelium lining the uriniferous tubules and be accompanied by hypertrophy of the left ventricle.

Liver.—A slight degree of hepatic cirrhosis is often present, and in some cases there is endarteritis and periarteritis as in other organs.

Lungs.—In the lungs no special changes have been observed, except in one case in which Boyce and Beadles found the walls of the alveoli, the septa, and the pleura thickened and loose in texture. Many of the alveoli were filled with a mucoid substance, and there was some round-celled infiltration of their walls.

Suprarenal Capsules.—The suprarenal capsules show no special changes. In one case scattered collections of small round cells and some fatty degeneration of the epithelial cells were observed by Hun and Prudden.

Muscles.—The condition of the muscles has not often been noted, but Dr. R. M. Buchanan of Glasgow in one case found that they were pale and soft and that their fibres were loosely held together.

Serous Effusions.—Effusions into the serous cavities are frequently found and a small amount of anasarca is not uncommon.

PATHOLOGY.

Chemical Pathology.—We have already seen that in secondary myxœdema in the monkey an excess of mucin has been found in various parts of the body. A similar but less marked excess has been observed in some cases of primary myxœdema in man. Dr. Ord was led to infer, from the character of the œdema observed during life and the absence of exudation from the skin when cut after death, that the unusual spaces which he observed between the bundles of fibrous tissue were filled with some gelatinous substance. The committee of the Clinical

Society regard these spaces as exceptional, and when present as identical with those seen in ordinary œdema. Cranstoun Charles made an analysis of the skin of the feet of Ord's first patient, who died in the swollen condition, and found that it contained more than fifty times as much mucin as healthy skin, or skin swollen by ordinary œdema. It was on account of this mucous nature of the œdema that Ord proposed the name myxœdema for the disease. Subsequent examinations of the skin have failed to show the presence of such a large excess of mucin. Prof. Halliburton, in reviewing the results of the analyses of the skin in myxœdema made by Stevenson, Bernays, and himself, points out that in only two was an excess of mucin found—in one 0·81 per cent. and in the other 0·72 per cent. The average of the ten analyses was 0·374 per cent., which, if anything, is slightly less than the normal amount in healthy skin, which has been estimated at 0·385 per cent. Halliburton considers that the amount of mucin found in these analyses was small, in some cases because the patient had died in the atrophic stage of the disease and in others because the specimens had been kept for a long time in alcohol before the analyses were made. In the swollen stage of the disease there is probably an increase of intercellular ground substance which yields an excess of mucin, which is not obtained in the late atrophic stages. In one case examined by Halliburton the tendo Achillis contained 1·42 per cent. of mucin, which is nearly three times as much as is found in normal tendons. In the cardiac tendons Halliburton has found, in each of four cases, a slight excess of mucin above the normal amount, and in one case, which had been under the care of Dr. Oliver, as much as 5·22 per cent., or

five times as much as is usually found in persons who have not suffered from myxœdema. In the same case the muscular substance of the heart contained 0·26 per cent. of mucin, whereas normal heart muscle contains only minute traces of it. Other organs of the body have been examined for mucin, but the results do not convey much information, as the amount in normal tissues has not as yet been ascertained. The parotid gland, which usually contains merely a trace of mucin, has been examined in only one case, in which the mucin was found to amount to 0·188 per cent., while the sub-maxillary gland of the same patient yielded 0·159 per cent. (Halliburton). No mucin has been found in either the blood or the urine, nor has any been discovered in the pericardial, peritoneal, pleural, or cerebro-spinal fluids.

General Pathology.—In dealing with the functions of the thyroid gland in Chapter I. we have already considered the facts which explain the pathology of myxœdema, so that a short summary only will be necessary here. We have seen that a condition of myxœdema, due to loss of thyroidal secretion, can be induced in lower animals by removal of the gland. In man secondary myxœdema is induced by removal of the thyroid gland, and the primary form is always accompanied by a destructive lesion of the gland, with diminution or cessation of its secretion. In animals the symptoms due to loss of thyroidal secretion can be removed by renewing the supply and so making good the loss. In describing the results of the treatment of myxœdema in man it will be shown that all the symptoms of primary and secondary myxœdema disappear, when thyroidal secretion is regularly supplied by internal administration, in sufficient quantity to make good the loss sustained by

the disease of the gland. These facts clearly show that myxœdema in man is entirely and solely due to disease or removal of the thyroid gland and the consequent failure of the supply of its internal secretion.

DIAGNOSIS.

In fully developed myxœdema the diagnosis is readily made on inspection by any one who is familiar with the characteristic aspect produced by the disease. Quite recently (1899), within a few days in the same street in Newcastle, I passed two cases of myxœdema so advanced that the disease could be easily recognised at a distance of several yards. The appearance in each case showed that the disease must have been in existence some time, probably several years, without treatment. In a well-developed case the full rounded face and wrinkled forehead, with flushed cheeks, swollen eyelids, thickened lips, and scanty hair form a striking picture. On further examination the solid subcutaneous swelling all over the body, and especially of the hands and feet, the dry skin, sub-normal temperature, and the various subjective symptoms described by the patient fully confirm a diagnosis suggested by the facial aspect. In the early stages of the disease the diagnosis is often much more difficult, as some of the characteristic symptoms just mentioned may be absent and others ill-defined.

The most striking changes in the appearance of these early cases may be due to an alteration in the complexion of the skin rather than in the expression of the face. Thus the yellowness of the skin of the face may be a striking feature, and accompanied, as it generally is, by the central pink flush in the cheeks it imparts a false appearance

of good health, as if the patient had spent much time in the open air in the country. When this appearance is seen in a patient, who has not been thus exposed, it should always lead to further inquiries being made for other symptoms of thyroïdal insufficiency. The presence of yellow subconjunctival fat I believe to be rare, though it may be mentioned in passing that I have seen all the fat in the body of a monkey, which died after thyroïdectomy, of this same golden yellow colour.

In these cases the subcutaneous swelling is as a rule only slight. The cheeks may appear rather full and the chin be rounded, changes which may readily be attributed to the presence of subcutaneous fat. Swelling of the subcutaneous tissues of the eyelids may be slight or absent altogether, while there may be no visible swelling of the nose, lips, or tongue, although elevation of the eyebrows with transverse wrinkling of the forehead may be present early. Consequently the change in the expression of the face and hands is not nearly so marked as in the advanced stages of the disease. The skin may be rather drier than usual, and there are frequently dry scaly patches over the knees and elbows, but in some cases at this stage the skin is still soft and moist, and at times there may be free perspiration. Some hair may have been lost, but often it is not more than might be expected, considering the age of the patient.

The subjective nervous symptoms are often striking. Complaint is made of lassitude, and fatigue is somewhat easily induced. Both visual and auditory hallucinations are not uncommon. The former take the form of ill-defined objects, sometimes thought to resemble mice or rats, rapidly crossing the floor, or rats and cats are distinctly seen running across the room, while brightly

coloured stars are also sometimes seen. Noises, such as bells ringing or voices, are heard. It is an interesting and suggestive fact that these hallucinations or subjective sensations resemble the aura of an epileptic fit; and although epilepsy is uncommon in ordinary cases of myxœdema I have on several occasions witnessed a typical epileptic fit in a monkey after thyroidectomy. Patients show a certain disinclination to speak of these sensations, although they are perfectly aware of their subjective nature. These nervous symptoms occurring in women between forty and fifty are sometimes mistaken for those which so commonly occur at the menopause, but from which it is of the greatest practical importance to distinguish them.

The temperature in these early cases is generally normal or only occasionally subnormal, consequently the cold is not felt nearly so acutely as in advanced cases. Another interesting point is that in some of these cases the thyroid gland can still be felt and is not appreciably diminished in size; in one of my cases it was even enlarged. When any doubt exists as to the diagnosis in one of these slight cases it can be cleared up by treating the patient for a few weeks with a daily dose of ten minims of thyroid extract. If the symptoms are the result of thyroidal insufficiency they will disappear. Some cases of myxœdema have a superficial resemblance to patients suffering from chronic nephritis and have in consequence been diagnosed as cases of Bright's disease. The resemblance is all the stronger in anæmic cases, in which the flush on the cheek is absent. One of my patients, who had lost blood from hæmorrhoids, strikingly resembled a case of chronic tubal nephritis in facial appearance. In the majority of these cases renal disease can be

excluded at once by an examination of the urine, which will be found to be free from albumin. It must, however, be remembered that albuminuria does occur in some cases of myxœdema. In such cases the albumin is small in amount and disappears with treatment by thyroid extract, and the urine does not contain casts, which signs serve to distinguish the albuminuria of myxœdema from that of Bright's disease. Renal cirrhosis may occur as a complication of myxœdema, but will be accompanied by other symptoms of renal disease, such as high tension pulse, hypertrophy of the left ventricle and abundant urine of low specific gravity. It is said that some cases of myxœdema have been exhibited in shows as "fat women," but as a rule myxœdema can be readily distinguished from ordinary obesity by the presence of other characteristic symptoms in addition to the subcutaneous swelling. In one of my cases (*vide* Fig. 16) the two conditions coexisted and it was only after a careful examination that the presence of myxœdema, as well as obesity, was determined, a conclusion which was confirmed by the beneficial results of thyroid treatment.

Another condition which might be mistaken for myxœdema is adiposis dolorosa, a rare disease first described in America by Dercum. I have only seen one case in this country. In adiposis dolorosa irregular masses of fat develop in various parts of the body, the swellings being preceded or accompanied by neuritic pains. It is distinguished from myxœdema by the fact that the face, hands, and feet are not involved, and by the presence of the pain and tenderness on pressure, which are absent in myxœdema.

Acromegaly can be distinguished from myxœdema by several important features. The face is long and oval

instead of rounded as in myxœdema, and the enlargement of the features is due to an actual increase in size of the bony and other structures and not to the accumulation of a subcutaneous swelling. In acromegaly the skin tends to be moist instead of dry and rough, and the hair abundant instead of scanty, as it so frequently is in myxœdema. In the former the enlargement is most noticeable in the hands and feet and upper ribs, and there is an actual increase in the size of the bones, whereas in the latter the increase in size is due to the solid œdema which occurs all over the body and is most marked in the soft parts.

PROGNOSIS.

The prognosis of myxœdema has been entirely changed by the introduction of the present method of treatment. Formerly a certain amount of temporary improvement or arrest of normal progress might be expected in summer, or during residence in a warm climate, and from the employment of diaphoretics, especially pilocarpine, massage, warm baths, and general tonics ; but sooner or later the disease would progress and directly or indirectly cause the death of the patient. Now all the symptoms of myxœdema can be removed within a few months by the regular administration of thyroid extract and any return of the symptoms prevented by the continuous use of the remedy. My first case, who began to be treated more than nine years ago, still takes one drachm of thyroid extract during each week and remains quite free from any symptoms of the disease ; this shows clearly that the freedom from myxœdema can be maintained as long as the patient lives. From this it follows that if

treatment is commenced before any incurable cardiac, arterial, or renal disease has developed, life should not be appreciably shortened by the changes in the thyroid gland. If the disease is of long duration or any complications have occurred, the prognosis is not so favourable and must be made according to the state of the patient at the commencement of treatment. The presence of advanced cardiac or arterial degeneration is always a source of danger, especially during the first stage of the treatment. With care this stage may be safely passed and then the prognosis must be based upon the actual condition of the circulatory system. Insanity increases the gravity of the prognosis, but it is not necessarily incurable, as several cases of the insanity of myxœdema have been cured by thyroid treatment. A temporary albuminuria, which disappears under treatment along with the other symptoms, does not materially affect the prognosis. If, however, there is persistent albuminuria, which is not influenced by treatment, and casts are found in the urine, the prognosis must be governed by the nature and gravity of the renal symptoms which are present.

TREATMENT.

In primary and secondary myxœdema in man we see the results of loss of thyroid secretion pure and simple and consequently are able to remove the symptoms entirely by giving a sufficient supply of the secretion. Soon after I first determined to try this method of treatment in myxœdema, I was fortunate enough to come across a well-marked case in a woman who, after the nature and experimental character of the treatment had been explained to her, was bold enough to give full permission for it to

be carried out whatever the result might be. This patient was shown at the February meeting of the Northumberland and Durham Medical Society in 1891, when the treatment of myxœdema by thyroid extract was first suggested and described by me. The treatment was commenced in the following April and the symptoms soon disappeared, proving the correctness of the conclusions which had led to the suggestion of the remedy. More than nine years have elapsed and this first case still remains free from myxœdema.

We may now briefly consider the method of carrying out this treatment of myxœdema. The main objects of the treatment are to remove the symptoms, by restoring normal metabolism as rapidly as possible without risk to the patient; and when this has been accomplished, so to regulate the treatment as to continue the supply of thyroid secretion in sufficient quantity, to maintain the normal rate of metabolism of the tissues generally. For this purpose the treatment is divided into two stages. During the first stage the tissues are gradually brought back to a normal condition. This may, according to the severity of the symptoms, require from one to three months. As soon as the symptoms have entirely disappeared the first stage is completed. The condition of the atrophied thyroid gland is not influenced by the treatment, so that if the artificial supply of secretion is discontinued, at this or any other time of the patient's life, all the symptoms of myxœdema will gradually return, as I have found by actual experience. Thus the second stage of the treatment of necessity lasts as long as the patient lives. It is therefore necessary to make the permanent daily dose as nearly as possible equivalent to the normal amount of secretion. If the dose falls below this, slight symptoms

of myxœdema will reappear, and if it is excessive a condition of thyroidism will be produced.

Preparations of Thyroid Secretion.—Thyroid secretion can be given in several different forms. The actual gland itself containing the secretion may be used, and is a useful form when the patient lives in some remote place or when it is necessary to make the treatment as inexpensive as possible. Arrangements can easily be made for the regular supply of one lobe of the thyroid gland of a freshly killed sheep twice a week, by a butcher who has once been shown where the gland lies and the ease with which it may be removed. From one-eighth to one-quarter of a lobe is a suitable daily dose of the sheep's gland, one-quarter of a lobe being equivalent to about ten minims of liquor thyroidei. As the raw gland is somewhat nauseous it should be minced and taken in glycerine or some similar vehicle in order to make it palatable, or it may be lightly cooked on the outside by frying or boiling before it is eaten. As a rule it is much better to employ one of the preparations of the thyroid gland rather than what may be termed the crude drug itself. Of these, two are now official, liquor thyroidei and thyroideum siccum, the former of which is simply my original liquid thyroid extract. The liquor thyroidei is the most convenient preparation for general use, and in my experience the most efficient. It is prepared from a considerable number of glands at a time, so that the strength is uniform. In prescribing, it should be ordered in the undiluted form and not more than a sufficient supply for a fortnight should be obtained at one time. This preparation is conveniently given in a single daily dose at bedtime. The patient must be provided with a minim measure glass and should measure out the dose of five or ten minims, as the case may be, adding

a dessertspoonful of water at the time it is taken. The dry thyroid of the Pharmacopœia, one grain of which is equivalent to six minims of liquid thyroid extract, may be given as a powder or made up into a pill or tablet in doses of one or two grains. If the dried preparation becomes damp it is liable to decompose and become unfit for use.

Method of Treatment.—In advanced cases the first stage of the treatment must be carried out with great caution, especially if any symptoms of degeneration of the cardiac muscle, such as attacks of syncope, dyspnœa on exertion, feeble or irregular pulse, or weak heart sounds are present. Under these circumstances the patient should be confined to bed at first and only small doses of from three to five minims of liquor thyroidei given each night. This dose if well borne may be gradually increased up to ten minims. If not confined to bed these patients are apt to make use of their returning vigour too soon, before the heart has had time to recover and to adapt itself to the altered conditions brought about by the treatment. These advanced cases in which little exercise has been taken for months or even years are now rare; but in the early days of the treatment the importance of this caution was painfully impressed upon me by the deaths of two patients, who had cardiac disease, from syncope after they had practically got rid of the symptoms of myxœdema. Any undue acceleration of the pulse up to ninety or one hundred indicates that a reduction should be made in the dose, and any signs of cardiac failure must be met by giving stimulants and digitalis. By far the greater number of cases which require treatment are now seen in the early stages of the disease before any cardiac symptoms have developed. In these the patient is able to go about as

usual, though it is advisable to avoid any unusual exertion, during the first stage of the treatment. A daily dose of ten minims of thyroid extract, or two grains of dry thyroid, may be given each night from the beginning and increased to fifteen minims at the end of a fortnight, if decided improvement has not already taken place. Any marked increase in the frequency of the pulse or rapid loss of weight is an indication for at once reducing the dose. Symptoms of gastro-intestinal catarrh have sometimes arisen during this first stage of the treatment, especially if the raw gland has been used. They rarely if ever appear if a suitable preparation of the gland is used instead. If they do occur the thyroid treatment should be stopped until they have passed away and then smaller doses should be given when the treatment is again commenced. In many cases no other treatment beyond the daily dose of thyroid extract is required. When, however, there is a well-marked anæmia it is a good plan to give iron as well as thyroid extract. Five grains of dried sulphate of iron in a pill twice or thrice daily after meals is a suitable form in which to give it.

As soon as all the symptoms of myxœdema have disappeared the first stage of the treatment is completed. The second stage then commences and must of necessity last as long as the patient lives. During this stage the patient must continue steadily to take a daily dose of thyroid extract equivalent to the daily output of the gland before it became diseased, or at any rate of that part of it which has become functionless. It is important that patients should understand this, and realise that good health can only be maintained by the continued use of the remedy. To ensure this it is often better to describe the remedy as an essential part of the daily diet and not as a

medicine, so as to overcome the objection some persons have to taking what they regard as a medicine for such long periods. Of course an occasional intermission of the treatment for a week or so has little or no effect, but if no thyroid extract is taken for three or four weeks the temperature falls one or two degrees below normal and the myxœdematous swelling of the face begins to develop again. If the extract is omitted for a longer period still all the original symptoms gradually reappear, till at the end of three or four months the condition will be much the same as it was before any treatment was adopted. The most suitable dose for the second stage of the treatment is, generally speaking, ten minims of the extract given once a day. If after a time any slight symptoms of myxœdema reappear the permanent dose should be increased to twelve or fifteen minims. In none of my own cases has it been necessary to give more than ten minims ; in a few cases this dose is too large, as after a time it produces acceleration of the pulse. The permanent dose has then to be fixed at five or seven minims a day. In doubtful cases of myxœdema thyroid extract may be given as a means of diagnosis. For this purpose a dose of ten minims should be given daily for three or four weeks. If the symptoms steadily diminish they are the result of thyroidal disease ; if, on the other hand, no improvement takes place they are due to some other cause. This test is of great use in distinguishing some of the cases with anæmia and subcutaneous swelling from cases of anæmia with ordinary obesity, which they often closely resemble.

Results of the Treatment of Myxœdema. — When the treatment of a well-marked case of myxœdema is carried out on the lines just indicated very definite and interesting results are soon obtained. One of the earliest signs of

improvement is the return of the temperature to the normal level. This is illustrated by one case in which the temperature before treatment ranged from 95° to 96° F., whereas during the second, third, and fourth weeks of treatment it varied between 96° and 98° (*vide* Fig. 20). As the temperature rises to normal the former sensitiveness to cold is lost and the frequency of the pulse is increased. The most striking changes are those which take place in the skin with its appendages and in the subcutaneous tissues. The myxœdematous swelling gradually disappears from all parts of the body, so that the face and hands once more assume their natural appearance and the free movement of the limbs, which has been considerably hampered by the swelling, is regained. The reduction of the swelling is accompanied by a loss of weight which may amount to as much as two or even four stones. The skin, which as a result of the removal of the swelling may for a time remain loose and wrinkled, becomes warm and moist owing to a renewal of the secretory activity of the sebaceous and sweat glands. Not infrequently there is some desquamation which may occur in fine scales or in large flakes from the palms of the hands and soles of the feet, as observed by Byrom Bramwell. The hair follicles resume their proper function, so that even where there has been complete baldness a good growth of hair is developed in the course of six or twelve months. Considerable changes are thus produced in the appearance of the patient, and they are well illustrated by the four photographs shown in Figs. 14, 15, 17, and 18, which illustrate the changes which take place in the appearance of the patient as the result of treatment. Fig. 15 was taken in 1892 after treatment for seven months and shows that the swelling has disappeared and

a good growth of hair has taken place. As already mentioned, this patient died from mitral disease in 1897, when the thyroid gland was found to be entirely converted into fibrous tissue and fat as was shown in Fig. 23.

In addition to these very obvious signs of improvement the feeling of lassitude passes away and normal muscular strength and activity are regained. As a result of this those who before treatment could barely walk a mile are enabled to walk long distances, climb mountains, and undertake various other forms of exercise. Mental processes become more active, the memory improves, and the hallucinations disappear. In some cases in which actual insanity had occurred it also has been cured. If albuminuria without actual renal disease has been present it disappears, while the amount of urine is increased. The observations of Ord and White show that the total amount of nitrogen eliminated is increased and that this increase is almost entirely due to the increase of urea in the urine. At first the amount of urea excreted may not only equal, but actually exceed, the normal average quantity. The number of red corpuscles in the blood increases. In patients who have not reached the menopause menstruation returns and takes place regularly, even when there has been amenorrhœa for several years. In fact the myxœdema is entirely cured, though the fibrosis of the thyroid gland remains unaffected by the treatment.

SECONDARY MYXCEDEMA.

Synonyms.—Cachexia strumipriva, operative myxœdema.

We have already seen that total removal of the thyroid gland in animals is followed by definite symptoms of

myxœdema. So also in man total removal of the gland for goitre has been followed by the development of typical secondary myxœdema identical with primary myxœdema, which results from fibrosis with atrophy of the gland. On September 13th, 1882, at a meeting of the Medical Society of Geneva, J. L. Reverdin drew attention to certain changes which he had observed to take place in some of his cases after total extirpation of the goitrous thyroid gland. The chief symptoms of this condition were weakness, pallor, anæmia, and œdema, without albuminuria, and he mentions that one patient closely resembled a cretin in appearance. On April 4th, 1883, at the twelfth congress of German surgeons, Kocher gave a very complete account of the symptoms which he had observed, with but few exceptions, to follow total removal of the thyroid gland for goitre, and to which he gave the name "*cachexia strumipriva*." This condition was considered by Kocher to be the result of injuries sustained by the tissues in the neck during the operation rather than the effect of the loss of the thyroid gland. Soon afterwards a further communication was published by J. L. and A. Reverdin in which attention was directed to the similarity between this condition, following total thyroidectomy, and myxœdema, which led them to name it "*myxœdème post-opératoire*." These authors pointed out that this peculiar condition was developed only after total extirpation of the thyroid gland, and rightly attributed it to the loss of that gland, a view which was afterwards adopted also by Kocher. The symptoms of the cachexia frequently begin to appear after the patient has recovered from the immediate effects of the operation; in some cases, however, no change has been observed until four or five months have elapsed.

In many cases the earliest symptoms are pains in the limbs and sometimes also in the shoulders, neck, and abdomen; these are soon followed by languor with weakness of the limbs, which, in the absence of early pains, may be the first symptoms to appear. Coldness of the hands and feet is complained of, especially in cold weather. Slowness of mental processes soon becomes a prominent feature, the speech is slow, and all voluntary movements are executed much more deliberately than before the operation. The sufferers are generally perfectly aware of the loss of their former activity. Swelling of the face, hands, and feet then takes place. The swelling may come and go for a time and then become permanent. It is most conspicuous in the eyelids and may cause pendulous swellings of the lower eyelids. As a result of the general swelling the features are much altered, the nose and lips become large and thick, and the whole face is broadened. The trunk also is increased in circumference by the swelling. The skin becomes dry and the hair also may be lost. The anæmia often becomes marked. In some cases headache, vertigo, tetany, and epileptic fits have been observed, which is not surprising considering the frequency of these symptoms in monkeys after thyroidectomy. In some cases there has been dyspnoea owing to narrowing of the larynx from paralysis of the abductor muscles; this is, however, a purely accidental complication, not due to the loss of thyroidal secretion, but to injury to the recurrent laryngeal nerves either by the operation or the subsequent contraction of the scar tissue formed in the wound.

From this description it will be seen that the clinical resemblance between cachexia strumipriva and primary myxœdema is complete. So striking is the similarity in

appearance between the two that Otto Lanz, who had often examined Kocher's cases of cachexia strumipriva, on seeing a photograph of one of the writer's cases of myxœdema in Newcastle, thought that it was taken from one of these cases which he had himself photographed in Berne! Kocher found that of thirty-two patients upon whom he had performed total thyroidectomy for goitre twenty-six developed the cachexia. The other six remained free from the cachexia, but in every one of them a return of the goitre developed either from a remnant of thyroid tissue, not removed at the time of the operation, or from an accessory thyroid gland. Thus in those cases in which sufficient thyroid gland tissue had been left no cachexia appeared, while the symptoms which developed in the others were evidently due to complete absence of the gland. The facts collected by the committee of the Clinical Society from a number of different surgeons showed that cachexia strumipriva had developed in about one-third of the cases in which apparently all active thyroid tissue had been removed, and in only a few cases after partial thyroidectomy. This evidence does not prove that the cachexia is due to the loss of thyroïdal tissue alone. When, however, we consider that these symptoms never follow any other operation involving the other important structures in the neck, it is evident that the cachexia when it develops is the result of removal of the thyroïdal tissue. Why it does not develop in all cases after total thyroidectomy we are not in a position to say. It seems likely that in these cases a portion of the gland tissue which has been left unobserved at the time of the operation, or an accessory thyroid gland, or even some other gland, has undergone sufficient compensatory hypertrophy to enable

it to carry on the functions of the gland which has been removed, and so prevent the onset of the cachexia. When the thyroid has been removed in early life arrest of development takes place in addition to the other symptoms, so that the patient becomes a cretin instead of developing the adult type of myxœdema as in the case already mentioned. The danger of inducing secondary myxœdema in man by total thyroidectomy has only to be known to be avoided, so that this operation is not now performed except in the case of malignant disease of the gland, and in a few cases of parenchymatous goitre in which multiple cysts have developed. In all other cases a sufficient portion of the gland is left to form an adequate supply of the secretion, so that secondary myxœdema now rarely if ever occurs. When total thyroidectomy is necessary the development of secondary myxœdema is easily prevented by the continuous administration of thyroid extract from the time of the operation.

CHAPTER III.

CRETINISM.

Derivation.—Crétin, Swiss patois for Chrétien, a Christian; or Latin creta, chalk.

Synonyms.—Infantile myxœdema, cretinoid idiocy. Latin: cretinismus; German: cretinismus; French: crétinisme, idiotie avec cachexie pachydermique, pachydermie crétinoïde.

Description.—Cretinism is here used solely to denote myxœdema arising in infancy or childhood before the age of fifteen. In older writings many cases were included under this name in which the arrest of development was not due to thyroidal disease and so were not really cases of cretinism at all. Here the term is only used to include cases of true cretinism, in which the symptoms are due to destructive disease or arrest of development of the thyroid gland, commencing before birth or in early life before the age of fifteen.

The general features of cretinism differ in many ways from those of myxœdema, for in addition to the symptoms which occur in the adult we have an arrest of mental and bodily development, the results of which become more and more apparent as the cretin grows older. A sharp distinction is often drawn between sporadic and endemic cretinism, the two conditions being described separately. Careful examination shows, however, that

the division is an artificial one and that they should not be separated. We do not give separate descriptions of enteric fever because it may occur in an endemic, epidemic, or sporadic form, as each of them is due to a common cause, infection by the typhoid bacillus. Both forms of cretinism are also the result of a common cause, a loss or diminution of the functional activity of the thyroid gland due to disease of that organ, and should therefore be considered as one disease. The actual lesion of the gland may vary in nature, causing either diminution or increase in the actual size of the gland, and it may vary considerably in severity, causing varying degrees of disablement up to total loss of function. The severity of the symptoms is proportional to the amount of destructive disease of the gland; the less the amount of secretion passing from the gland into the blood the greater the severity of the symptoms, just as in myxœdema in the adult.

ETIOLOGY.

The loss or diminution of function of the thyroid gland, which is the cause of cretinism, may be due to (1) absence of the gland, (2) arrest of its development, (3) fibrosis with atrophy of the glandular substance, (4) conversion into goitre, (5) removal by operation. Our knowledge of the actual condition of the gland is at present scanty, but as far as it goes it tends to show that in cases of cretinism where the symptoms are present at birth they are due to an absence or arrest of development of the gland. In these cases in which the child is healthy at birth, but begins to show signs of cretinism during the first few years of life, it is evident that the gland has

been fully formed at first, but subsequently a fibrosis with atrophy has developed, in all probability of the same character as that we have already described in the adult. Goitrous degeneration is common in endemic cretinism but rare in the sporadic form. As in the case of the adult, the exciting cause of the destructive disease of the gland is at present unknown. At most we know something of the conditions under which the disease arises and which may act as predisposing causes.

Age.—Cretinism may develop in utero or at any time between birth and the age of fifteen years. In some cases the cretinism is so far advanced in utero that the child is born dead, in others the symptoms are only partly developed at birth and become more marked afterwards. These two congenital varieties of cretinism are, however, rare. As a rule nothing abnormal is noticed about the child at birth, but at some time during the first three or four years the symptoms first attract attention. In exceptional cases the symptoms do not appear until the eighth or even the twelfth year.

Sex.—Cretinism occurs more frequently in the female than in the male. This is brought out clearly in any large series of cases. Out of 9 cases which I have seen, only 2 were males, while 15 out of an additional 36 cases of which I have collected records were males. Osler has published a series of 23 male and 35 female cretins; Bramwell has tabulated 14 of the former and 30 of the latter, and Langdon Down 3 male and 8 female cases. By adding all these together we obtain a series of 158 cases, 57 of which were males and 101 females. So that the disease occurs nearly twice as often in the female as in the male. Fletcher Beach in a

series of 116 cases found that there were not quite twice as many females as males.

Heredity.—Sporadic cretinism does not appear in two successive generations, for the simple reason that cretins of both sexes are nearly always sterile. There is no evidence to show that the children of parents who have subsequently become myxœdematous are more liable to the disease than others. The disease may, however, appear in two or more children of the same family. Thus a brother aged five and a sister aged eight were brought to see me together, both suffering from cretinism. Bramwell quotes an instance recorded by Stirling in which three girls and one boy in a family of eleven were cretins, and another example is given by Caverley in which two brothers and a sister were cretins. In some cases the parents have been neurotic, tuberculous, or alcoholic, but no great stress can be laid upon the presence of such common conditions as predisposing factors. Poor circumstances such as have been present in some cases do not favour the development of the disease in my experience, as they were absent in seven out of nine cases I have seen. In endemic cretinism heredity certainly comes into play, as the disease often develops in the children or grandchildren of those who have suffered from endemic goitre.

Locality.—Sporadic cretinism, unlike the endemic form, is not confined to certain localities, but occurs alike in Europe, America, and Australia. In Great Britain cases of sporadic cretinism occur in many parts of the country. In a few districts the disease is more prevalent than in others and may be described as endemic. Thus in the upper valleys of the Pennine Range, in the North of England, in the neighbourhood of Alston, Stanhope, and

Kendal, where goitre is endemic, there are a considerable number of cretins. At Chiselborough, in Somerset, in 1847, no less than twenty-four out of a population of three hundred and fifty were cretins; but the disease has since died out. In endemic cretinism locality plays an important part, as this form of the disease is most frequently found in the narrow valleys of mountainous districts of Europe and Asia. The exciting cause of the disease is evidently closely allied to, and probably identical with, that of endemic goitre, which will be discussed more fully in considering that disease. The evidence we so far possess all goes to show that the local cause for both conditions is to be found in the drinking-water, which is, however, rendered harmless by boiling. We do not know what this constituent of the water may be, though the destructive action of heat seems to show that it may be a living organism. The interesting feature about the poison, whatever its nature may be, is that it usually requires at least two generations to produce cretinism, goitre appearing in the first generation subjected to its influence and cretinism only in the second or third. Thus Fagge mentions that it has been observed that when a healthy family migrates into a district where both goitre and cretinism are endemic, goitre may develop in the first generation, but cretinism only in the second or third generation. It appears also that some waters may produce goitre alone, while others, presumably owing to greater activity of the same constituent, cause both goitre and cretinism. St. Lager gives a remarkable example of this in the village of Antignano (Asti), in which there were three wells. The families which used the first well contained both cases of goitre and cretinism; in those who lived near the second only cases of goitre occurred;

while the rest of the inhabitants, who used the third well, were quite free from both diseases. Another well-known example of the influence of the drinking-water, mentioned by Ewald, is that of the parish of Bozel, in Savoy, the population of which in the year 1848 was 1,472, and included 109 cretins and 900 cases of goitre. The neighbouring parish of St. Bon, which was similar in all respects except that the water-supply came from a different source, was free from cretinism. A fresh water-supply for Bozel was then obtained from St. Bon, with such good results that in 1864 there were only 58 cretins and 39 cases of goitre in Bozel.

SYMPTOMS.

The appearance of a cretin is so unique and striking that in a well-marked case it can be recognised at once. The early stages of the disease may easily be overlooked or the mother may state that even at birth the child did not look quite natural. In other cases the child appears to be quite normal at birth, and to remain so for the first few months, year, or even two years of its life. Then it is noticed that the child is growing less rapidly, and is less bright and active than other children of the same age. Some change in its appearance may also be observed at the same time, for which medical advice is sought. When the symptoms are well marked it is at once apparent that mental and bodily development are both much retarded, if not arrested.

Nervous System. *Mental Symptoms.*—The child when awake sits or lies languidly in one position, doing nothing, for many minutes at a stretch, and appears to take no interest in its surroundings, presenting a strong contrast

to the constant activity of a healthy child. It can, however, be roused from this hebetude by the sight of a familiar face or of food, and the powers of recognition are generally good for members of the family. The mental condition varies considerably in different cases. Young cretins are dull, placid, and inactive, characters which are still more marked in the adult, whole hours of the day being spent sitting still, either playing with some simple toy or doing nothing at all, as all evince great dislike to bodily activity. Some cretins are so deficient in mental powers as to be quite helpless idiots: some as they grow older remain in much the same condition as in childhood; they are able to feed themselves, use a few simple words, and are clean in their habits, but show no more signs of intelligence than a healthy child of one or two years of age. Others, again, show more intelligence and their mental powers are capable of still further improvement by suitable education. The expression is generally stolid and fixed, but most cretins are easily amused and made to laugh. They nearly always sleep well, and for longer periods than healthy individuals of the same age. The power of speech in older children and adults varies according to the mental condition: in some cases it may simply consist of unintelligible sounds; in many cases, however, words of one syllable are used, and, aided by signs, the wishes are readily communicated to those who are familiar with the patient. In slight cases speech may be but little affected, though the voice itself is often hoarse. In idiotic cases the habits, as might be expected, are dirty. I have seen one female case, only three years of age, in which there was frequent masturbation. When there is a moderate amount of intelligence cretins are usually careful and cleanly.

Special Senses.—Sight is generally quite good, but the sense of smell is often deficient. Hearing is often imperfect, as many as two-thirds of the cases examined by the Sardinian Commission showing this defect.

Motor Power.—Motor power is generally deficient, and young cretins are late in learning to crawl and may not be able to walk alone until they are four or five years old. When able to walk the gait is slow and awkward and all voluntary movements are executed slowly and deliberately.

General Condition and Appearance.—The whole body is short and stunted, and the older the patient the more striking the discrepancy between age and size. Thus in one of my cases, in which the symptoms had first appeared before she was a year old, the height at the age of twenty-eight was only $34\frac{1}{2}$ inches. There is a general subcutaneous solid œdema, which varies in amount in different cases. This swelling, though general in distribution, is most evident wherever the subcutaneous tissues are lax, as in the eyelids, lips, cheeks, and neck, and especially in the supraclavicular fossæ, where it often forms definite rounded swellings, the so-called “fatty tumours” on each side of the neck. The back of the hand and the dorsum of the foot are also much swollen in many cases. The head is narrow in front and broad behind, the anterior fontanelle remains patent, and Wormian bones may be present in the sutures of the skull. The forehead in some cases is wrinkled transversely. The face as a whole is rounded, owing to the swollen condition of the cheeks and chin, which may be loose and pendulous. The eyes appear to be widely separated, while the nose is short and broad, depressed at the bridge, turned up at the tip, and the nostrils

dilated. The mouth is generally open and looks large, the lips being much thickened and everted, while the large swollen tongue frequently protrudes between them. The ears are large and prominent. The complexion is uniformly pale, no dilated venules being visible on the cheek as in myxœdema in the adult, and the mucous membrane of the lips is opaque and often cyanosed. The skin is dry and rough, owing to the absence of cutaneous secretions, and feels cold to the touch. At the flexures of the joints it is often thrown into folds and creases by the subcutaneous swelling. Flat pigmented moles and warts are often present on the face and elsewhere in adult cretins. The scalp is often rough and covered with dry brown crusts ; the hair upon it is generally fairly abundant, though coarse in texture, while in adult cretins it is very scanty, if not entirely absent on the eyebrows and on other parts of the body. The nails may be rough, thickened, and cracked. The teeth are late in developing and are often carious. The neck is short and thick, an appearance which is accentuated by the large amount of solid œdema present in the supra-clavicular fossæ. In the majority of cases no thyroid gland can be felt in the neck ; in a few it can be felt and appears to be about the normal size ; exceptionally it is found to be enlarged. There is generally well-marked lordosis of the lower dorsal and lumbar spine, which may also be deformed by angular or lateral curvature. The abdomen is large and prominent ; in many cases either an umbilical or inguinal hernia is present. The limbs are short, owing to the arrest of growth of the long bones, and may be wasted from muscular atrophy, or swollen, if there is much solid subcutaneous œdema. The hands and feet especially are broad and thick.

The above features combined in an advanced case make up a picture of repulsive ugliness rarely surpassed in the worst of nightmares, which reaches its climax in the adult cretin, which has aptly been called a "pariah of nature." In addition to the symptoms already described the temperature is generally one or two degrees below normal and the pulse and respiration are slow. Severe attacks of syncope, in which the patient is unconscious and pulseless, are not uncommon in cases of long duration. A greater or less degree of anæmia is generally present, and the hæmoglobin in the blood may be reduced to half the normal amount. In one case Lebreton and Vaquez found that the red corpuscles were larger than normal and that some of them were nucleated. If this condition is found to be common it would indicate that the blood, like other tissues, is arrested in development and retains some of its foetal characteristics. Constipation is usual in cretins of all ages. In adults there is a marked arrest of development of the generative organs in both sexes. The testicles, ovaries, uterus, and mammae are no more developed than in the child, and hairs are almost entirely absent from the pubes and axillæ. Sexual instincts are in abeyance, and menstruation is either absent altogether, or only occurs at long and irregular intervals, when the discharge is very scanty. The following case, which I have had the opportunity of seeing several times during the last few years with Dr. Bunting of Scotswood, is a good example of advanced cretinism in the adult, the onset having occurred in infancy.

A single woman, aged twenty-eight years, was first seen in June 1895. In infancy the mother noticed that the extremities became blue and cold after washing, and

that the abdomen was prominent. After a fall in which the back was hurt, at nine months of age, growth became arrested and the symptoms of cretinism gradually developed. The patient now has the symptoms of advanced cretinism. She is only $34\frac{1}{2}$ inches in height, and the head looks relatively large, the forehead being broad and flat. The anterior fontanelle is not quite closed by bone, though it has a dense thick covering which yields but slightly when firm pressure is made. The hair is dark, fairly abundant, and coarse, but it grows well. The scalp is dry, rough, and scaly. The appearance of the face, body, and limbs, shown in Fig. 24, is very characteristic. The expression is generally dull and fixed, but a broad grin appears at once if she is amused. The skin has a yellowish tint, but there is a slight flush in each cheek. All parts of the face are very considerably swollen, especially the eyelids, cheeks, and lips. The nose is short, broad, and turned up at the end. The mouth is large, the lips being thick and everted. The tongue is large and generally protrudes from the open mouth. The teeth are ill-developed and carious. The mother thinks that she has never yet lost her first set of teeth. The ears are large and prominent. The neck is short and thick, and no trace of a thyroid gland can be felt. The subcutaneous swelling forms a soft elastic pad just above each clavicle. The abdomen is protuberant, and there is a small umbilical hernia. The limbs are all short and stunted in appearance. There is well-marked lordosis of the spine. Both feet and hands are swollen and cold. The skin as a whole is dry and rough. There are two pigmented moles, one on the chest and the other on the cheek. The mammary glands are rudimentary, like those of a child, and there is no pubic



FIG. 24.

CRETIN, BEFORE TREATMENT, AGED 28,
JUNE, 1895; HEIGHT, $34\frac{1}{2}$ IN.

hair. Menstruation has only occurred a few times and the flow has been very scanty. Her temperature is 96.3° F. at 3.30 p.m. She cannot read, write, or even dress herself. She can feed herself if inclined, and sleeps well. She can walk slowly, but rarely leaves the house, and may be left alone in a chair without moving for two hours. The vocabulary is limited to a few words, such as "Ma," "Thomas," and "Pussy." She is easily amused and sometimes has fits of almost uncontrollable laughter.

The appearance of the patient in whom the symptoms of the disease had been present for twenty-seven years is shown in Fig. 24. Systematic treatment was at once commenced and the result will be detailed later.

NATURAL COURSE AND TERMINATION.

The consideration of the symptoms of cretinism has already shown that the natural course of the disease, when untreated, is extremely slow. The symptoms develop gradually, so that it is often difficult to fix the time of the onset even approximately. When once the symptoms have become fully developed the condition may remain practically unchanged for years together. Thus in the case just related there had been very little mental or physical change in the patient for twenty years. A considerable number of cases die during the first few years of life, not so much perhaps from the cretinism itself as from some acute intercurrent disease to which they can offer but a feeble resistance. The general tendency in all cases is sooner or later to get gradually worse, and no spontaneous improvement, with the exception of a slight temporary remission of some of the

symptoms during the warm weather, ever occurs. Those cases which survive the earlier years of childhood may, however, attain the age of twenty, thirty, or even forty years. Some endemic cretins attain even a greater age, and on the whole they appear to live longer than sporadic cretins, who rarely reach forty. This is probably due to the fact that a much larger proportion of the former have goitre, and consequently the function of the thyroid gland is not so much impaired as in cases in which there is fibrosis with atrophy of the gland, as in the majority of sporadic cretins. This point, however, requires further investigation, as I know of no actual statistics to prove that goitrous cretins live longer than the others. Death may occur from some acute intercurrent disease, such as pneumonia, to which cretins easily succumb, or it may be the result of chronic renal disease or cardiac failure.

MORBID ANATOMY.

Our knowledge of the pathological anatomy of cretinism is still very deficient, as but few complete post-mortem examinations have as yet been recorded. The chief interest attaches to the diseased condition of the thyroid gland, upon which the other changes depend.

The Thyroid Gland.—In describing the condition of the thyroid gland it is most convenient to follow the plan adopted by Rushton Parker and by Osler and to divide the cases into three classes: (a) with absence of thyroid gland, (b) with atrophy of thyroid gland, (c) with goitre. In adopting this grouping it is important to bear in mind that the essential lesion is impairment or loss of the function of the thyroid gland, which may be due to any one of the three conditions named, and that in each

group the actual degree of failure of the function of the gland may vary from a slight insufficiency, associated with a minor degree of cretinism, up to total abolition of function with severe cretinism.

(a) *With Absence of Thyroid Gland.*—In some cases no trace of a thyroid gland has been found after death ; in such the gland has either not developed at all or has become so completely wasted as to leave no remains. This absence of the gland was first observed by Curling in two cases of cretinism fifty years ago. In sixteen out of one hundred and sixteen cases collected by Fletcher Beach a post-mortem examination was made, and in fourteen no thyroid gland was found ; in the remaining two cases the gland was goitrous. In the records of ten autopsies collected by Bramwell it is stated that the gland was absent in nine. Osler also records a case reported by Dr. Friend, in which not even a trace of fibrous tissue could be found in the site of the gland.

(b) *With Atrophy of the Thyroid Gland.*—In these cases there is a distinct history of good health for several years in early childhood, followed by the development of symptoms of cretinism. The thyroid gland is normal at birth, remains so for several years, and then a fibrosis with atrophy develops, just as in myxœdema in the adult. The thyroïdal disease may come on insidiously without apparent cause or may follow an attack of some acute infective disease. Thus cases have been recorded in which the symptoms developed after measles, whooping cough, enteric fever, and scarlatina with nephritis. It is important to note that in these cases in which the disease commences in later childhood just the same condition was established as in Sick's case after removal of the gland for goitre

at ten years of age, which will be referred to again. The actual condition of the thyroid gland has been ascertained in only a few of these cases, and though there were slight differences between them the more important morbid changes were the same in all. The changes have been well described by De Coulon, Hanau, and Barker. The gland is diminished in size, and on section a large increase of fibrous connective tissue is apparent to the naked eye. With lower powers of the microscope the fibrous tissue separating the lobules and surrounding the alveoli can be seen to be greatly increased in amount. With higher magnification this thickened stroma is seen to consist largely of white fibrous tissue with but few nuclei, while in places, where the glandular structures show signs of rapid atrophy, the nuclei are more numerous. There may be a few cysts lined by glandular cells and filled with colloid. The alveoli of the gland show marked degenerative changes and can be seen in various stages of atrophy. In some the lumen is diminished or obliterated entirely, and very few contain any colloid. The epithelial cells are irregular in size, some being considerably larger than normal, and both cell protoplasm and nuclei show degenerative changes. In places where the atrophy is still more advanced the alveoli are only represented by small groups of epithelial cells surrounded by the newly formed connective tissue. It will thus be evident that in the main the changes are similar to those which are found in myxœdema in the adult, and consist essentially of a fibrosis of the whole gland, with various degrees of atrophy of the glandular secreting structures, leading to great diminution, if not to complete arrest, of function.

(c) *With Goitre*.—Comparatively few sporadic cretins have goitre, in which respect they differ from endemic

cretins, in whom goitre frequently occurs. Of 116 cases of sporadic cretinism collected by Fletcher Beach only 7 had goitre, and of 60 cases collected by Osler in America 7 had goitre, or in other words only 8 per cent. of sporadic cretins have goitre; whereas of 5,923 cases of endemic cretinism collected by the Sardinian Commission 3,912, or 66 per cent., had goitre; so that goitre occurs eight times as frequently in endemic as in sporadic cretinism. We have no information as yet as to the structure of the goitre when present in sporadic cretinism. There can, however, be no doubt that, whatever the exact nature of the enlargement may be, it, just as much as the fibrosis with atrophy, entails destruction of the secreting portion of the gland.

Skeleton.—The skeletal changes have been observed more closely in the endemic than in the sporadic form of the disease, but in all probability the changes are the same in each. The total length of the skeleton is much less than in an average child or adult of the same age and sex. Adult cretins are rarely more than $4\frac{1}{2}$ feet high, and not infrequently they measure less than 3 feet during life, as in the case already described, in which the height was only $34\frac{1}{2}$ inches at twenty-eight years of age. The long bones are short and thick, and may be bent and deformed, like the bones in rickets. Flattening of the condyles of the femur has been observed by Klebs, and Bircher found the neck of the bone thick and short and the head broad. The pelvis may be narrow as in rickets. Examination of the epiphysial cartilages at the ends of the long bones shows, however, that instead of the increase in the proliferation and columnar zones of the cartilage, which is seen in this situation in rickets, there is an arrest of its development, and Grawitz found in one

typical case that all signs of columnar formation of the cartilage cells were absent. The peculiar shape of the skull, which is seen in many cretins, was attributed by Virchow to a premature ossification of the spheno-occipital suture, which he found had already taken place in a newly born cretin, whereas normally it is deferred till the fifteenth year. The same condition was found by Grawitz in a seven months' foetus. This premature synostosis of the basi-occipital and basi-sphenoid bones, when present, would limit the proper growth of the base of the skull, while the membrane bones of the vertex continue to grow, so that the skull becomes short and broad. This early symptom does not, however, occur in all cases, for Bircher has found these bones still ununited as late as the twenty-fourth year. Too much stress has probably been laid upon this early ossification of one suture as a cause of the peculiar shape of the cretin's skull, which is rather a result of a general arrest of its proper development as a whole. Thus the typical skull of a cretin is short and broad and retains some of its foetal characteristics. The anterior fontanelle may remain widely open, and Horsley mentions that Wormian bones are often found in the sutures.

PATHOLOGY.

We have seen in the preceding section that the essential lesion in cretinism is absence or destructive disease of the thyroid gland, just as in myxœdema in the adult. In considering the functions of the thyroid gland in Chapter I. we showed what a profound influence upon the growth and development of young animals was produced by removal of the gland at an early age, and that in fact a condition

of cretinism can be produced by this operation in lambs and kids. In addition to this we have the valuable evidence afforded by the case recorded by Bruns, in which a boy, from whom Sick had removed an entire goitre at the age of ten, became a complete cretin. We know also that in the treatment of cretinism, when the supply of thyroid secretion is renewed by giving thyroid extract, the symptoms are removed. These facts conclusively prove that cretinism is entirely due to disease or arrest of development of the thyroid gland and the consequent deficiency of its secretion in the blood.

DIAGNOSIS.

In an advanced case of cretinism the arrest of mental and bodily development, combined with the striking appearance already described, are so characteristic that a diagnosis can generally be made by inspection alone. In slight cases in young children diagnosis is sometimes more difficult; but a history of arrest of development should always raise the suspicion of the existence of cretinism, which will be confirmed if there is inability to walk or talk, delay of dentition, combined with some subcutaneous swelling, a vacant expression with thickened lips, open mouth, and protruding tongue. In doubtful cases the therapeutic test is of great assistance, and in such, systematic treatment by thyroid extract should be carried out for two or three months. If no decided improvement has then taken place the child is evidently not a cretin, for in other forms of arrested growth the treatment has comparatively little effect. The importance of early diagnosis in such cases lies in the fact that the earlier the treatment is commenced the better prospect

there is of normal development of the central nervous system.

Mongolian Idiocy.—Some types of idiocy may be mistaken for cases of cretinism. The Mongolian idiot most nearly resembles a cretin on account of the stunted growth and mental defect. In both there is also depression of the bridge of the nose and protrusion of the tongue, the temperature is subnormal, the abdomen is prominent, an umbilical hernia may be present, dentition and speech are both delayed, and the anterior fontanelle is late in closing. The cretin differs, however, from the Mongolian idiot in the following points: he is dull and apathetic, slow in movement, and the face is expressionless, whereas the Mongolian idiot is smiling and observant, and shows more active movements, while the characteristic changes found in the skin and hair of the cretin are absent. In a doubtful case the therapeutic test will be followed by rapid improvement if the child is a cretin, and by little or none if it is a Mongolian idiot. There are, however, some cases which appear to be Mongolian idiots with cretinism; in such improvement of those symptoms which are due to thyroïdal insufficiency will be observed, but not in the others.

Achondroplasia.—Another rare condition which has been mistaken for cretinism is achondroplasia, a disease which is especially characterised by arrest of growth of the diaphyses of the long bones with enlargement of their epiphyses. Thus achondroplastic dwarfs have short and stunted limbs, the bridge of the nose is depressed, and the hands and feet are short and thick. In these dwarfs the relative shortness of the limbs and the length of the trunk are striking even in early infancy, whereas in infant cretins this is not the case, the disproportion only becoming

evident later on. They may also be further distinguished from cretins by the following characteristic features: The mental condition is not deficient, while the skin and hair are natural in appearance. The abdomen is not protuberant, while the buttocks are often prominent. There are no supraclavicular swellings, the temperature is normal, and if the thyroid gland can be felt it will be found to be normal in size. Dr. J. Thomson has also shown that the hands, though short, differ from those of a cretin in showing a distinct parting between the second and third fingers, which curve away from one another.

PROGNOSIS.

Formerly the prospect for a cretin was indeed a gloomy one, for we have already seen, in considering the natural course of the disease, that no recovery took place and sooner or later the disease ended fatally. Even in cases where life was prolonged for years the condition of mind and body was such as to render the life of a cretin a mere existence, without profit or pleasure to himself or any one else. Since the introduction of our present rational method of treatment the prognosis is much more favourable. In fact we may go as far as to say that if a case is recognised as early as possible, and treatment is commenced at once and continued steadily without interruption, physical development may continue as rapidly and as fully as in a normal child. Under these conditions it may, in the absence of any history of the case, be impossible to tell from the physical condition of the child after treatment that it has ever been a cretin. The mental development in many cases is not so good, as even when the physical development is all that could be desired the

mental condition is no better than that of a child several years younger. It is thus, even under the most favourable conditions, much more easy to foretell physical improvement than to gauge the amount of mental development which may be possible in any given case. The longer the disease has been in existence, before the commencement of treatment, the less the amount of improvement which can be expected ; but even in cases of many years' duration a remarkable amount of physical development may still be possible. Experience has already shown that in cretinism of some years' duration, rapid as the improvement in the physical condition may be, the intellectual development is much slower, so that when treatment is commenced late it is doubtful if the latter will ever advance as far as when treatment is started early.

TREATMENT OF CRETINISM.

We have already considered the results of athyroidism in young animals and children, and have seen how they are more serious than in the adult owing to the arrest of development. The treatment of a cretin consequently presents a more formidable task, but the results are in some respects even more interesting than in the adult. I would again point out the importance of carefully considering the possibility of the presence of disease or lack of development of the thyroid gland in every case of arrest or delay of development in children. In all such cases it is important to look for slight signs of cretinism. There are of course other causes of arrest of growth, such as achondroplasia ; but I have seen several cases where the ordinary symptoms of cretinism were not distinct and might easily escape observation if

not searched for carefully, in which the rapid improvement following thyroid treatment has proved that the arrest of development was due to thyroidal insufficiency.

The treatment of early cretinism is carried out on the same lines as the treatment of myxœdema in the adult. During the first stage gradually increasing doses of thyroid extract are given till the symptoms disappear. It is advisable in treating a small cretin to begin with a dose of one or two minims each evening, gradually increased by the addition of one minim each week or fortnight until a dose of five, seven, or ten minims, according to the size of the child, is reached. As the child gets older it may be found necessary to increase the daily dose from time to time by the addition of another minim. If too large doses are given the pulse becomes too frequent, pains may be felt in the limbs and elsewhere, the temperature may rise above the normal level, and purging may follow. As in the adult the treatment must be continued as long as the patient lives. As soon as the symptoms have disappeared it is only necessary to determine the most suitable permanent dose and to ensure its uninterrupted administration.

In the treatment of cretinism which has lasted for some years we have a much more difficult task to perform, but very good results can be obtained. Even when the disease has already lasted ten or twelve years, provided the patient is not more than eighteen or twenty years old, a remarkable amount of growth can take place. In these cases from three to five minims of thyroid extract may be given at the commencement and increased according to the progress observed. Even in cases in which the symptoms have lasted for twenty or twenty-five years some growth and marked improvement in all the symptoms

take place. In cases of long duration attacks of syncope are not uncommon. In such the earlier part of the treatment is more safely accomplished by keeping the patient in bed and giving small doses of one or two minims only at first.

Results of the Treatment of Cretinism.—When the necessary stimulus to the normal metabolism of growth is thus supplied to a cretin in the early stages of the disease the symptoms disappear. The swelling gradually diminishes in all parts of the body. The tongue, lips, and nose diminish in size, so that the appearance becomes natural. The skin becomes soft and moist and the temperature rises to normal. Growth, which at this early stage will only have been partially arrested, starts afresh. If the treatment is continuously carried on in such a case from the earliest time at which the disease is recognisable, there seems no reason to doubt that ultimately the child will grow up into a fully developed healthy adult who, however, would of course at any time develop symptoms of myxœdema if the supply of thyroid extract was discontinued. The amount of improvement which may take place in very advanced cases is well illustrated by the further course of the case described and shown in Fig. 24. In this case the symptoms had been present for some twenty-seven years before treatment was commenced. The dose was at first one drop a day, and has been gradually increased till now she takes fifteen drops, equal to about twelve minims of thyroid extract daily. At the commencement of the treatment growth had been arrested, apparently for many years, as she only measured $34\frac{1}{2}$ inches in height. She now measures $38\frac{1}{2}$ inches, having grown four inches in three and a half years. The hair is much less coarse than it used to be, and the scalp is white and smooth. The



FIG. 25.
CRETIN, AFTER TREATMENT, FEB., 1899 ;
HEIGHT, $38\frac{1}{2}$ IN.

swelling has greatly diminished, so that the nose, cheeks, and lips are much smaller than they were, and the whole expression is much more bright and intelligent. The mouth is kept closed and the tongue has become normal in size and no longer protrudes between the lips. The condition of the teeth does not seem to have improved except that she can now crack nuts, which she was unable to do before. The elastic pads have disappeared from the supraclavicular regions. A most remarkable development of the mammary glands, which before treatment were entirely undeveloped, has taken place. This is well shown in a recent photograph (Fig. 25), in which it will be seen that the nipples and breasts are now very well developed. Some pubic hairs have grown, and menstruation which had only occurred very scantily on a few occasions is now regular and abundant. The abdomen is less prominent and the umbilicus is retracted. There is still marked lordosis. The skin is much less dry and perspires freely when she is walking. She is much more energetic and the muscular strength has increased so that she can now walk two miles. The temperature has long been normal. She is distinctly more intelligent; her vocabulary has increased; she can recognise people and animals, and can make her wants perfectly understood. She is unable, however, to frame a sentence, and uses only single words, or at most two or three together. She is careful and cleanly in her habits.

This case is a good example of the amount of improvement of which even the worst cases are capable. Greater improvement still has been obtained in cases of some years' duration in which the patients are still under twenty years of age. Thus in Dr. John Thomson's patient, aged eighteen years and eight months, 33½ inches

in height, there was an increase in the height of $4\frac{3}{8}$ inches in twelve months ; and in Dr. Byrom Bramwell's patient, aged sixteen years and four months, $29\frac{1}{2}$ inches high, growth was at the rate of $6\frac{1}{2}$ inches in six months.

The intellectual development is always much slower than the bodily growth and general improvement in all other respects. The shorter the duration of the symptoms has been at the commencement of the treatment the more rapid the improvement in the mental condition, and I think it is only in cases in which the treatment is started early that we can expect normal intellectual development to take place. In cases of some duration it is important that a special education should be carried on at the same time as the treatment, in order that the patient may be able to make the most of the renewed cerebral activity.

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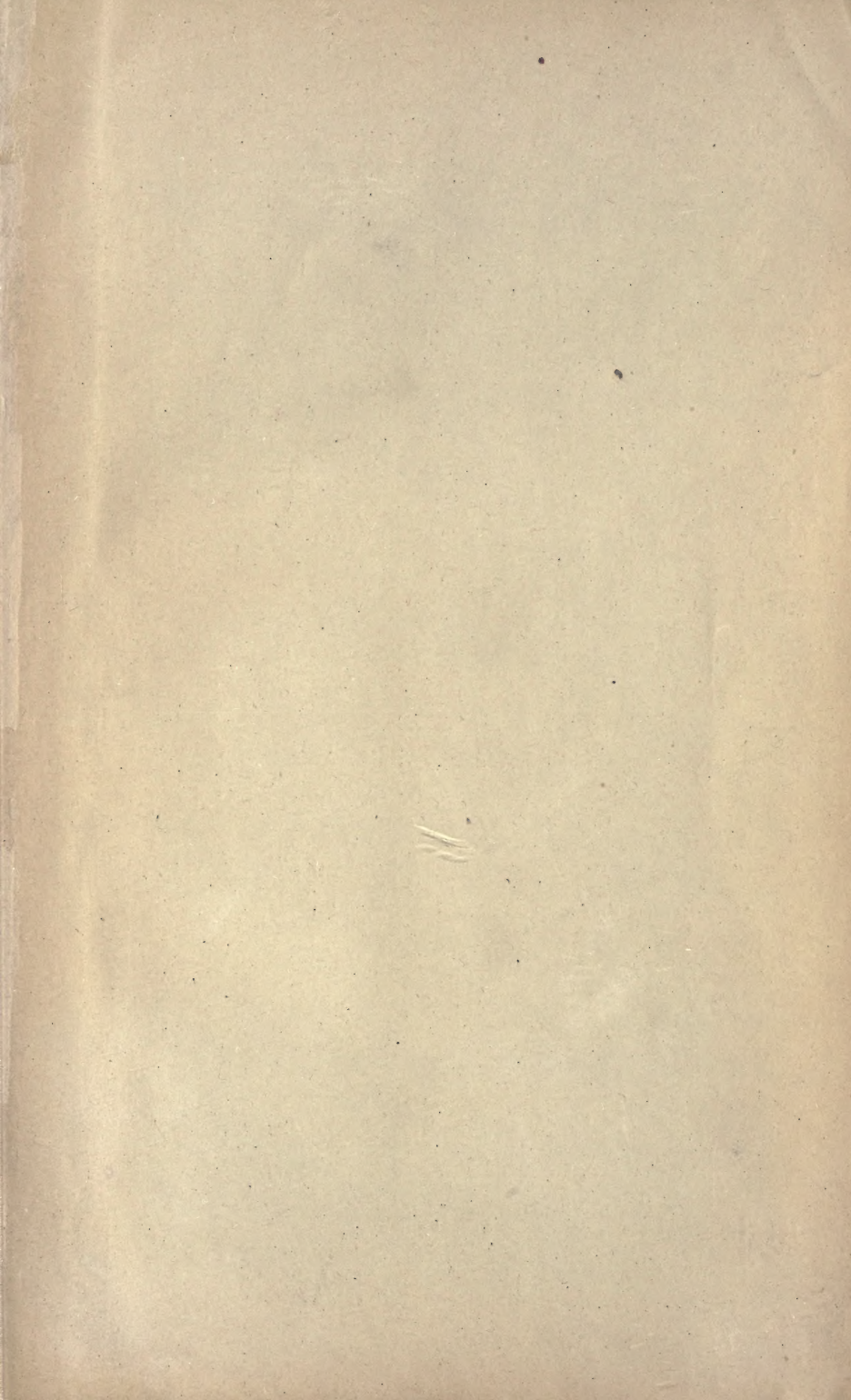
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